Four mechanisms to learn: S_N2 vs E2 and S_N1 vs E1

S = substitution = a leaving group (X) is lost from a carbon atom (R) and replaced by nucleophile (Nu:)

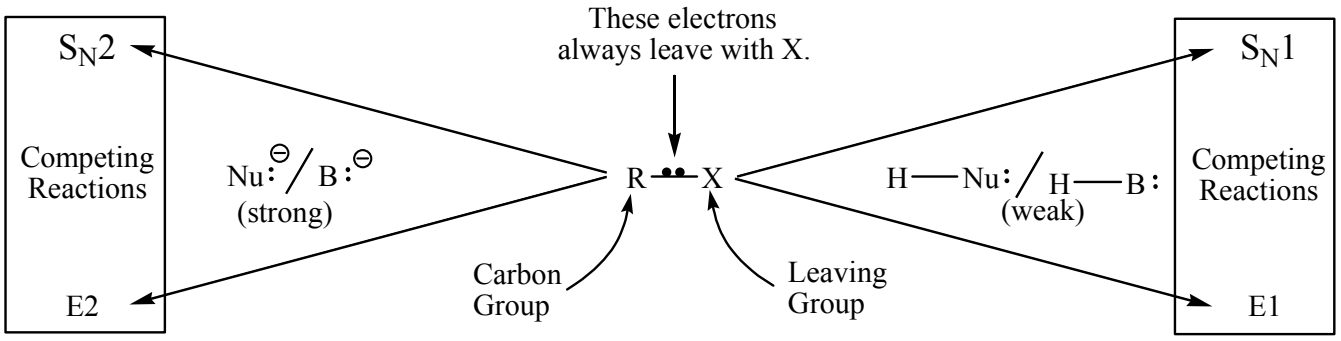
N = nucleophilic = nucleophiles {Nu:) donate two electrons in a manner similar to bases (B:)

E = elimination = two vicinal groups (adjacent) disappear from the skeleton and are replaced by a pi bond

1 = unimolecular kinetics = only one concentration term appears in the rate law expression, Rate = k[RX]

2 = bimolecular kinetics = two concentration terms appear in the rate law expression, Rate = k[RX] [Nu: or B:]

S_N2 competes with E2
S_N1 competes with E1



Nu: / B: = is an electron pair donor to carbon (= nucleophile) or to hydrogen (= base). It can be strong (S_N2/E2) or weak (S_N1/E1).

R = methyl, primary, secondary, tertiary, allylic, benzylic

X = -Cl, -Br, -I, $-OSO_2R$ (possible leaving groups in neutral, basic or acidic solutions)

X = $-OH_2^{\oplus}$ (only possible in acidic solutions)

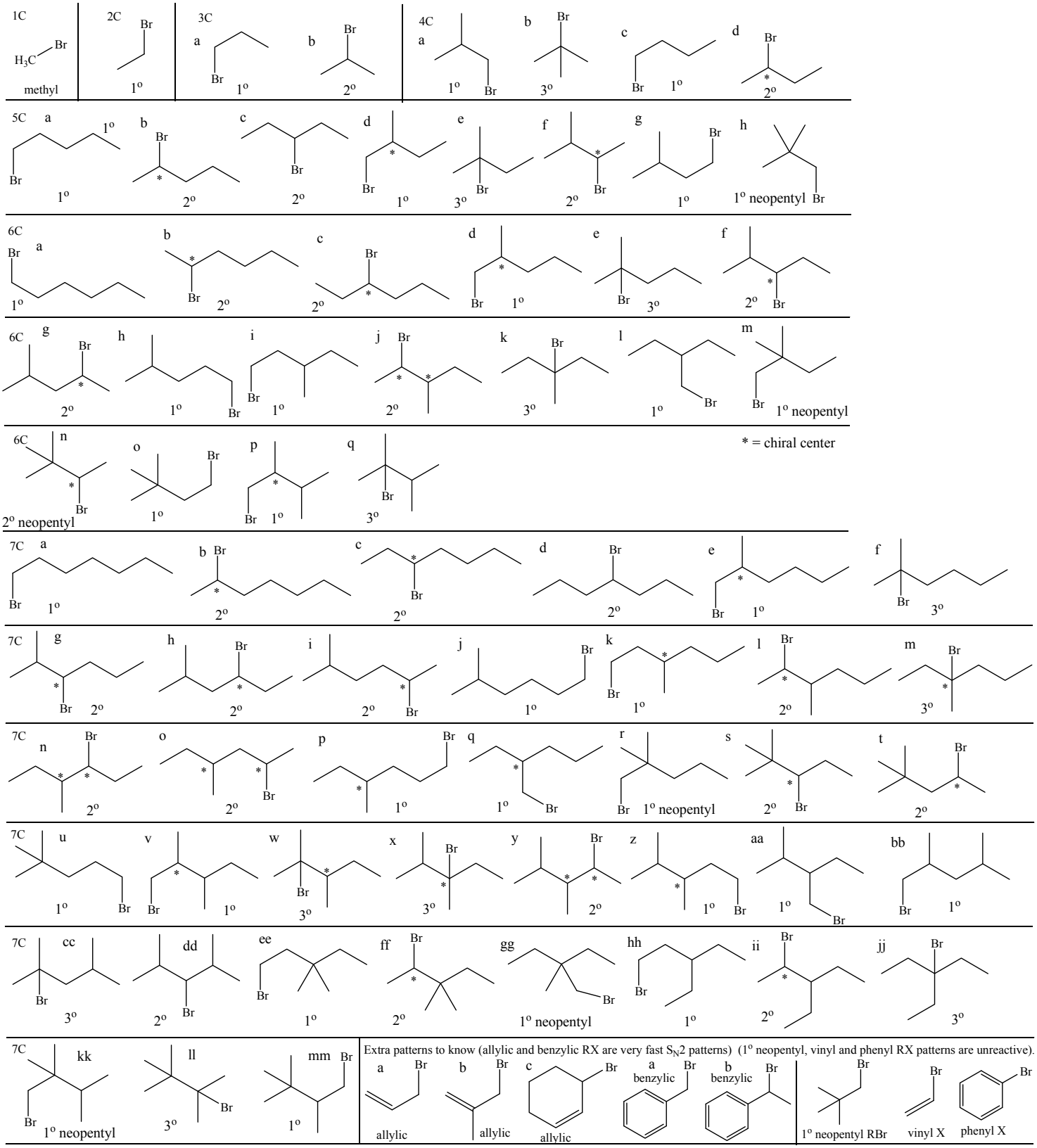
Important details to be determined in deciding the correct mechanisms of a reaction.

1. Is the nucleophile/base considered to be strong or weak? We simplistically view strong electron pair donation as coming from anions of all types and neutral nitrogen, sulfur and phosphorous atoms. Weak electron pair donors will typically be neutral solvent molecules, usually water (H_2O), alcohols (ROH), mixtures of the two, or simple, liquid carboxylic acids (RCO_2H).

2. What is the substitution pattern of the R-X substrate at the C_α carbon attached to the leaving group, X? Is it a methyl, primary, secondary, tertiary, allylic, or benzylic carbon? What about any C_β carbon atoms? How many additional carbon atoms are attached at a C_β position (none, one, two or three)?

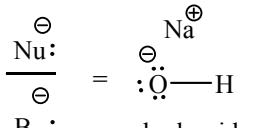
Answers to these questions will determine S_N2, E2, S_N1 and E1 reactivities and alkene substitution patterns and relative stabilities in E2 and E1 reactions.

R-Br examples C1 → C7 (infinite possibilities exist)

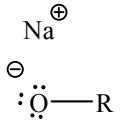


Strong electron pair donation in our course (S_N2 / E2).

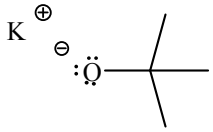
S_N2/E2 ⟶ concerted reactions (one step) S_N2 = always backside attack at C_α (inversion of configuration) E2 = anti C_β-H / C_α-X elimination (forms pi bonds)



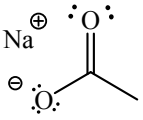
hydroxide (buy)



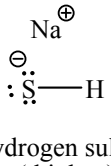
alkoxides (make)



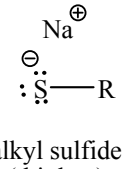
potassium t-butoxide (make, strong base)



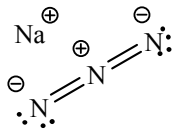
carboxylates (make, acetate)



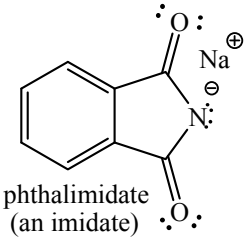
hydrogen sulfide (thiolate) (buy)



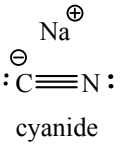
alkyl sulfide (thiolate) (make)



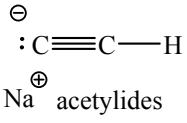
azide (buy)



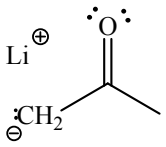
phthalimidate (an imidate) (make)



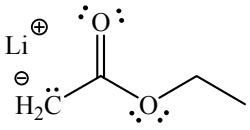
cyanide (buy)



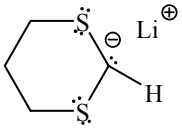
acetylides (make)



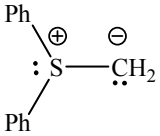
ketone enolates (make)



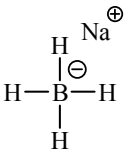
ester enolates (make)



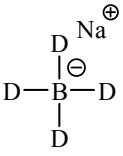
dithiane anion (make)



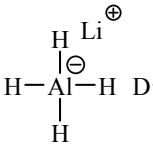
sulfur ylids



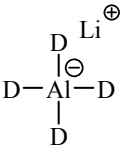
sodium borohydride (buy)



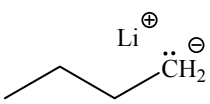
sodium borodeuteride (buy)



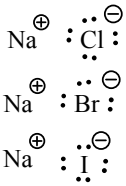
lithium aluminium hydride (buy)



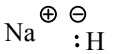
lithium aluminium deuteride (buy)



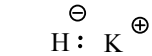
n-butyl lithium (very strong base or nucleophile, use anytime) (buy)



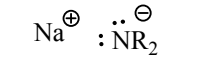
good nucleophiles with tosylates and in strong acid (buy)



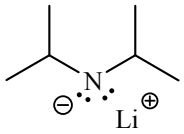
sodium hydride (very strong base) (buy)



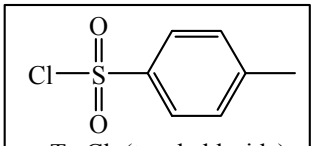
potassium hydride (very strong base) (buy)



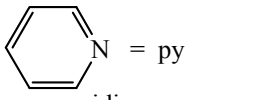
R = C or H sodium amide (very strong base) (buy)



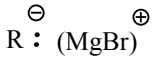
lithium diisopropylamide (very strong base) (make)



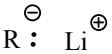
= Ts-Cl (tosyl chloride) makes ROH into tosylates



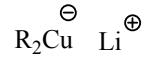
pyridine = proton sponge (buy)



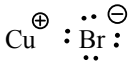
Grignard reagents (very strong bases and nucleophiles) (make)



alkyl lithium (very strong bases and nucleophiles) (make)

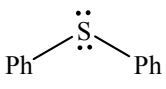


organocuprates (good carbon nucleophiles) (make)

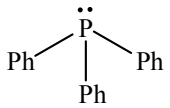


cuprous bromide (buy)

Important additions for us.



diphenylsulfide, used with C=O to make epoxides



triphenylphosphine used with C=O to make alkenes

Ph = phenyl

CrO_3 / pyridine

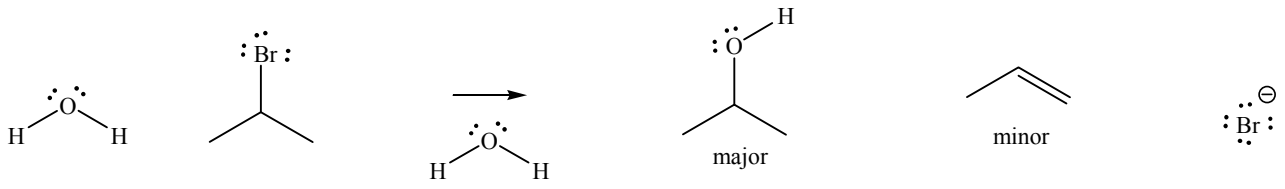
pyridinium chlorochromate PCC oxidizing E2 reaction (buy)

CrO_3 / H_2O

Jones reagent oxidizing E2 reaction (buy)

These two reactions look similar, but there are important differences.

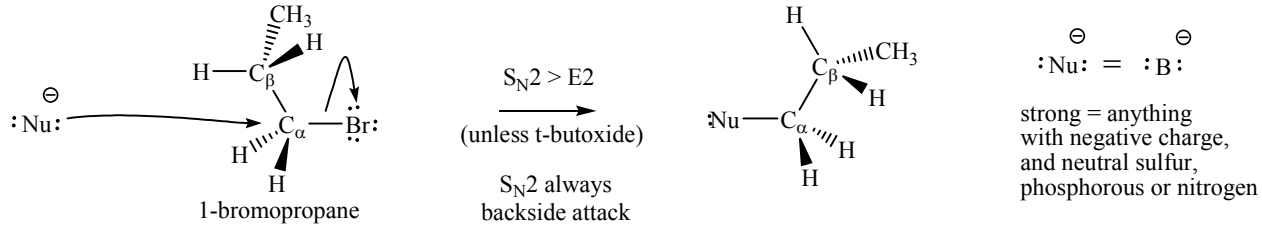
Rate = $k_{SN2}[HO^{\ominus}]^1[RBr]^1$ Rate = $k_{E2}[HO^{\ominus}]^1[RBr]^1$

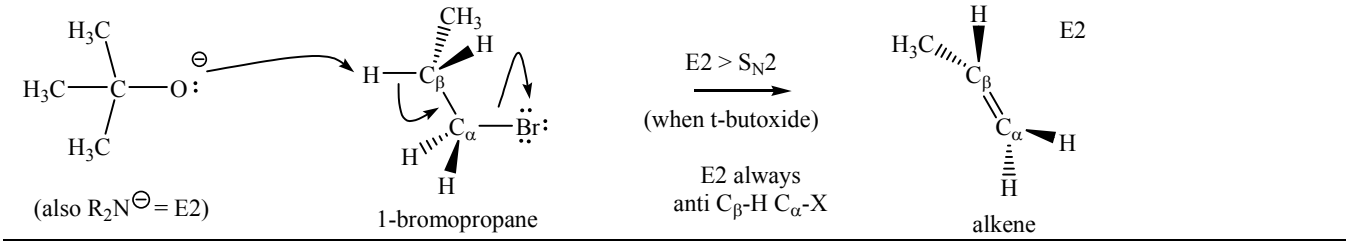


Rate = $k_{SN1}[RBr]^1$ Rate = $k_{E1}[RBr]^1$

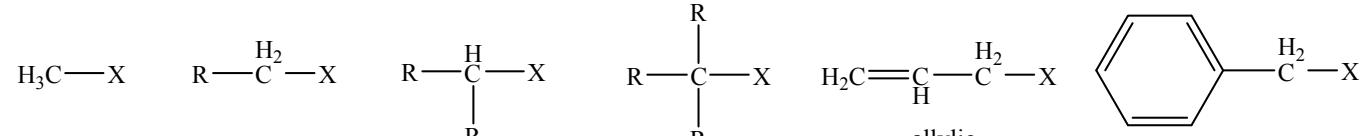
S_N2 versus E2 overview (essential features)

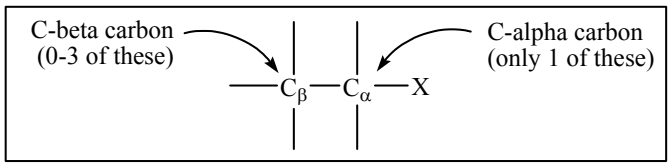
Example: 1° RX, requires strong nucleophile/base, S_N2 > E2, exceptions: potassium t-butoxide or sodium amide.



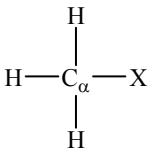


S_N2 reactions are the most important reactions – always backside attack at C_α-X carbon

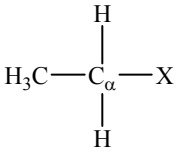




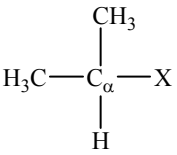
Relative rates of S_N2 reactions - steric hindrance at the C_α carbon slows down the rate of S_N2 reactions.



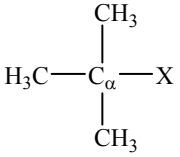
k ≈ 30
methyl (unique)



k ≈ 1
ethyl (primary)
reference compound

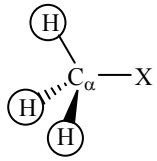


k ≈ 0.025
isopropyl (secondary)
$\left(\frac{1}{40}\right)$



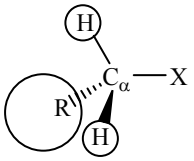
k ≈ 0
t-butyl (tertiary)
(very low)

methyl RX



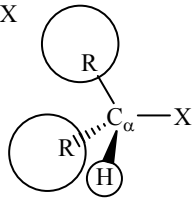
Methyl has three easy paths of approach by the nucleophile. It is the least sterically hindered carbon in S_N2 reactions, but it is unique.

primary RX



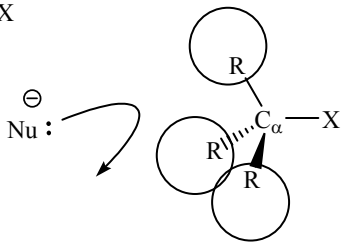
Primary substitution allows two easy paths of approach by the nucleophile. It is the least sterically hindered "general" substitution pattern for S_N2 reactions.

secondary RX

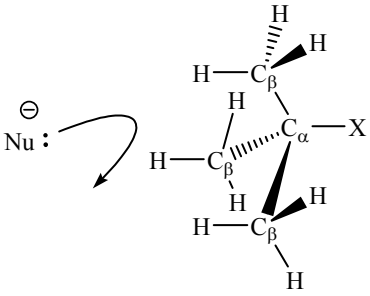


Secondary substitution allows one easy path of approach by the nucleophile. It reacts the slowest of the possible S_N2 substitution reactions.

tertiary RX

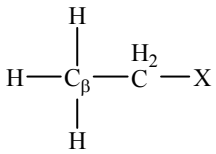


Tertiary substitution has no easy path of approach by the nucleophile from the backside. We do not propose any S_N2 reaction at tertiary RX centers.

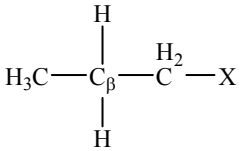


When the C_α carbon is completely substituted the nucleophile cannot get close enough to make a bond with the C_α carbon. Even C_β-H sigma bonds block the nucleophiles approach.

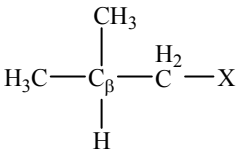
All of these are primary R-X structures at C_α, but substituted differently at C_β.



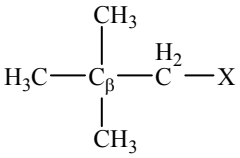
k ≈ 1
ethyl
reference compound



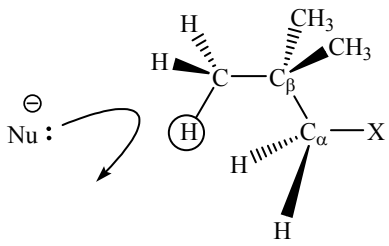
k ≈ 0.4
propyl



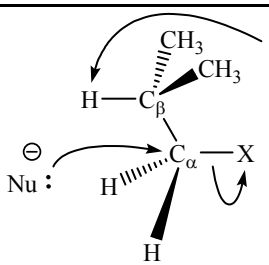
k ≈ 0.03
2-methylpropyl



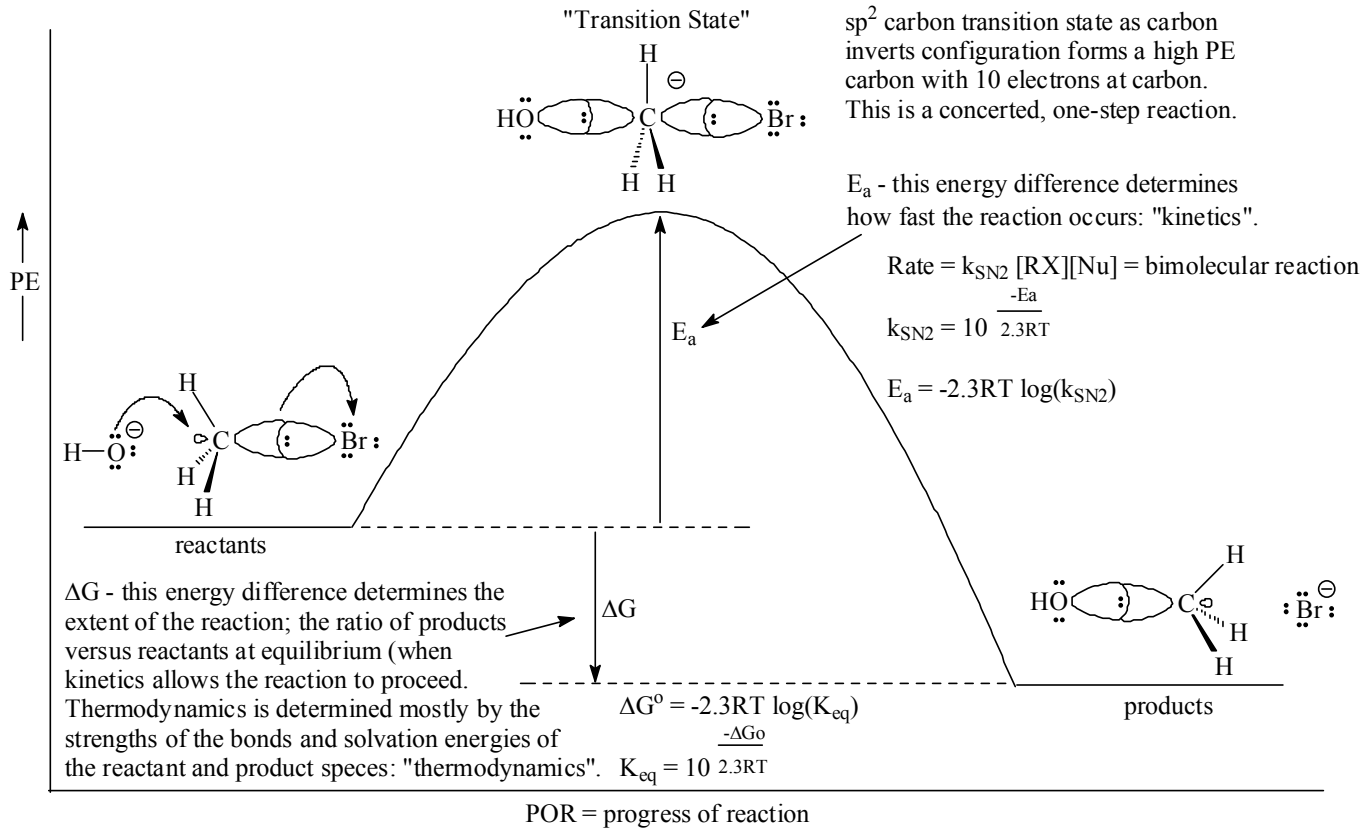
k ≈ 0.00001 ≈ 0
2,2-dimethylpropyl
(1^o neopentyl)



A completely substituted C_β carbon atom also blocks the Nu:⊖ approach to the backside of the C-X bond. A large group is always in the way at the backside of the C_α-X bond.

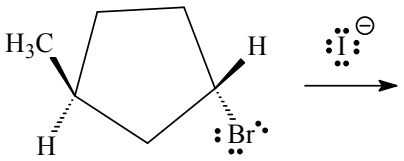


If even one bond at C_β has a hydrogen then approach by Nu:⊖ to the backside of the C_α-X bond is possible and an S_N2 reaction is possible.

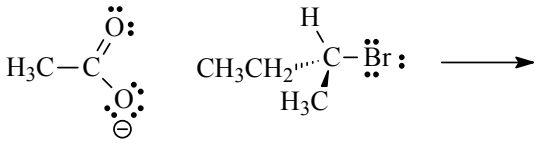


Problem 1 - How can you tell whether the S_N2 reaction occurs with front side attack, backside attack or front and backside attack? Use the two molecules to explain you answer. Follow the curved arrow formalism to show electron movement for how the reaction actually works.

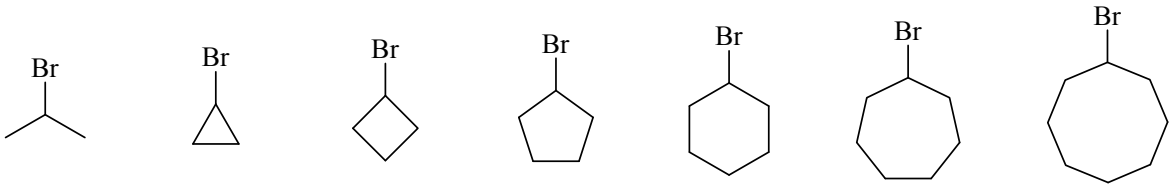
a



b

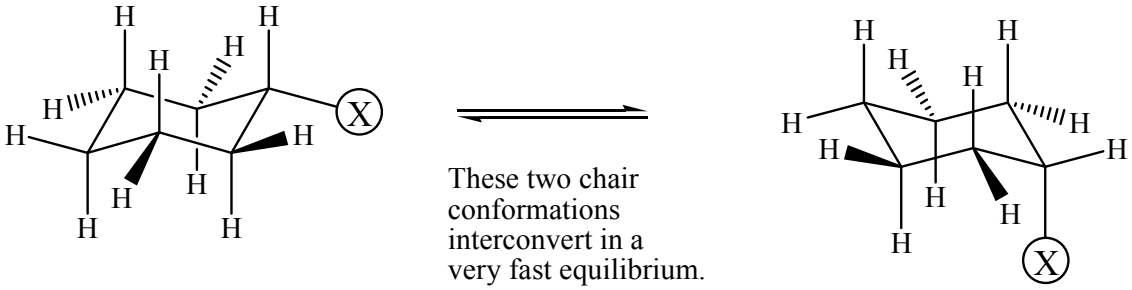


Problem 2 - Why might C_3 and C_4 rings react so slowly in S_N2 reactions? (Hint-think about bond angles in the transition state versus bond angles in the starting ring structure.)



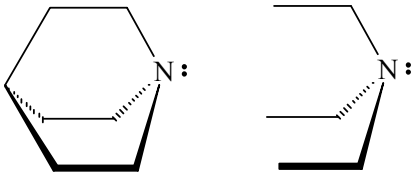
$k_{relative}$ (S_N2)	1.0	0.00001	0.008	1.6	0.01	0.97	0.22

Problem 3 - Why might C_6 rings react slower in S_N2 reactions? What are the possible conformations from which a reaction is expected? Trace the path of approach for backside attack across the cyclohexane ring to see what positions block this approach. Which chair conformation would have the leaving group in a more reactive position (axial or equatorial)? Is this part of the difficulty (which conformation is preferred)?

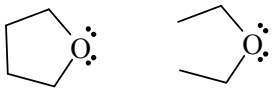


Problem 4 - In each of the following pairs of nucleophiles one is a much better nucleophile than its closely related partner. Propose a possible explanation.

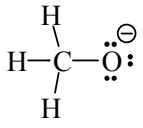
a. relative rates ≈ 250/1



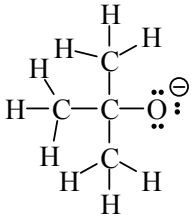
b.



c.

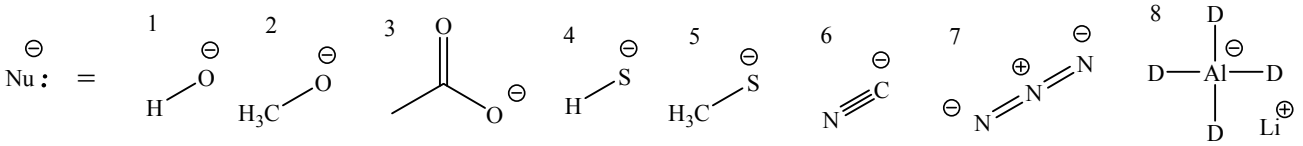


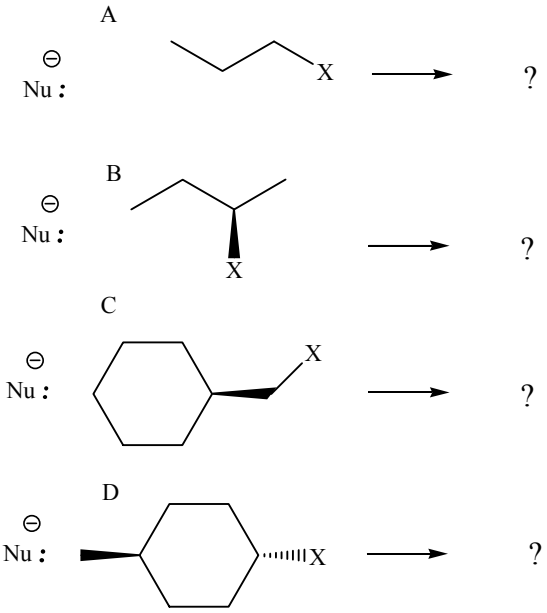
methoxide



t-butoxide

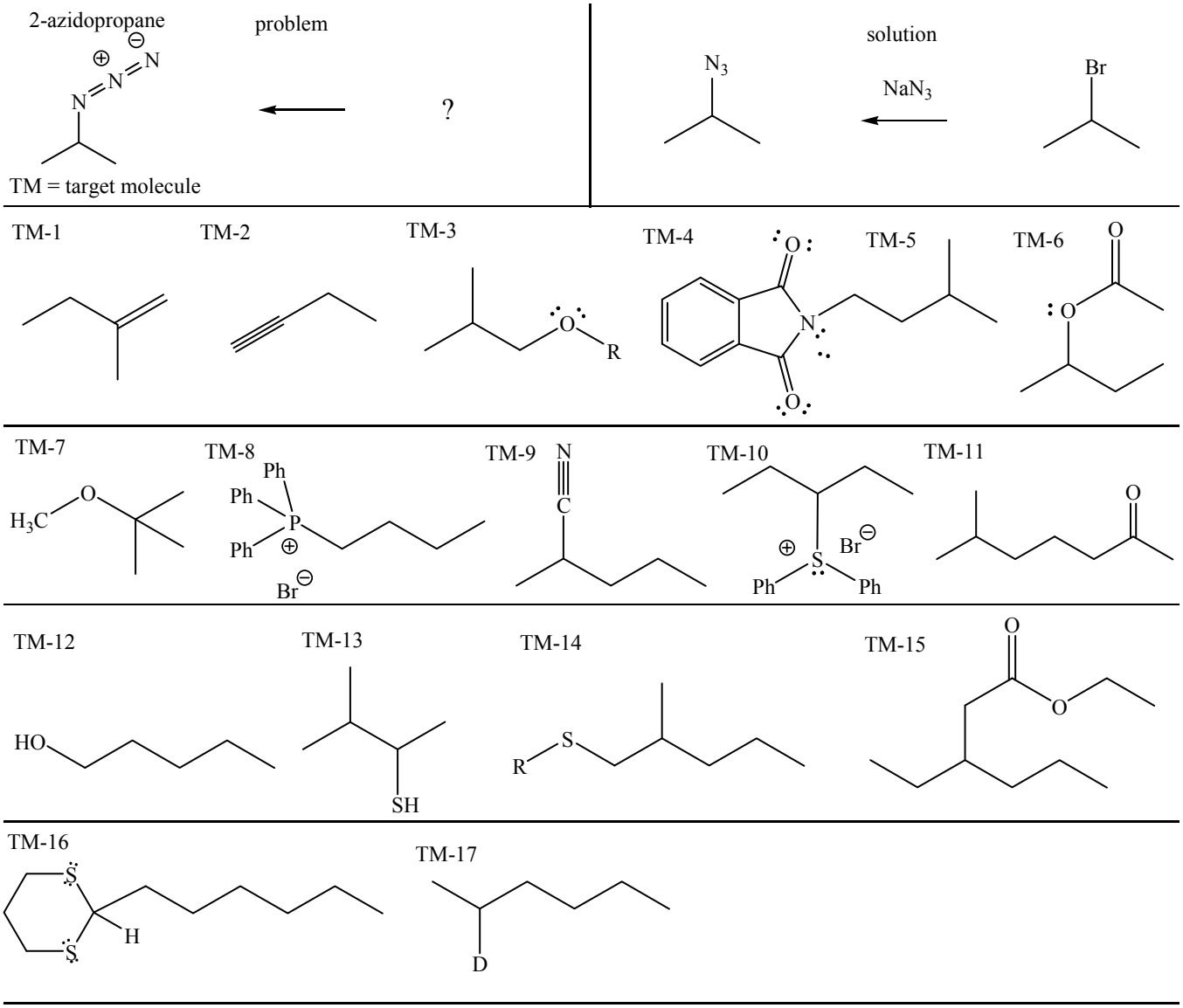
Problem 5 – Write out the expected S_N2 product for each possible combination (4x8=32 possibilities).





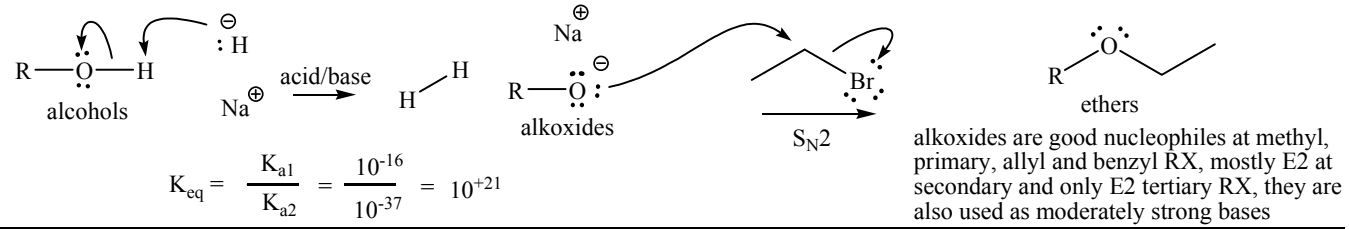
X = $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$ ...a good leaving group

Problem 6 – Using R-Br compounds from page 2 and reagents from page 3 to propose starting materials to make each of the following compounds. One example is provided. TM-1 is an E2 product (see page 15), all the others are S_N2 products.

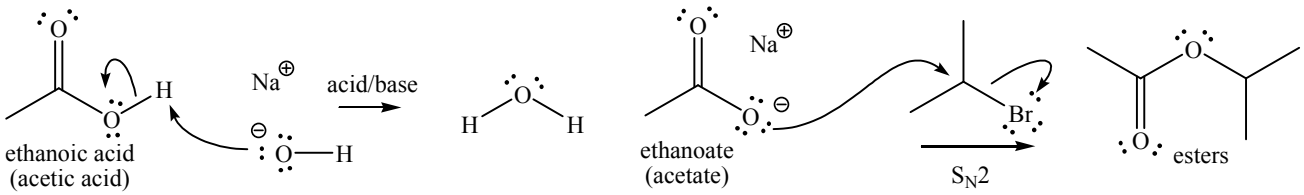


Acid/base reactions important to our course (some reagents have to be made, often by acid/base reactions) and subsequent reactions (mostly S_N2)

Make alkoxides and use as nucleophiles only at Me-X and 1° RCH_2-X in S_N2 reactions.



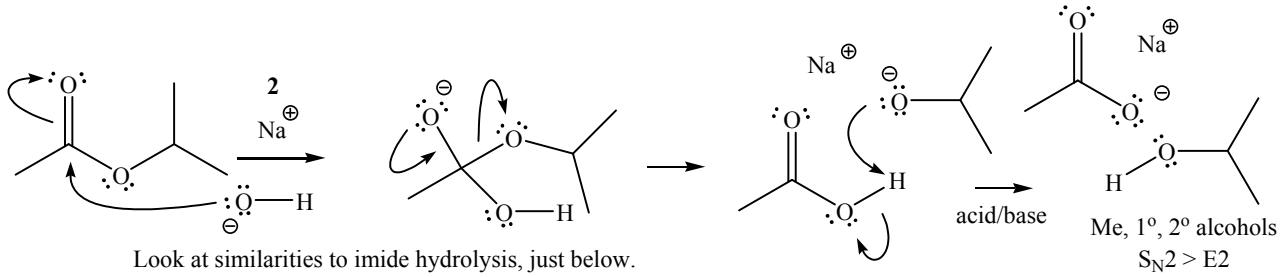
Make carboxylates and use as nucleophiles at Me-X, 1° RCH_2-X and 2° R_2CH-X in S_N2 reactions.



$$K_{eq} = \frac{K_{a1}}{K_{a2}} = \frac{10^{-5}}{10^{-16}} = 10^{+11}$$

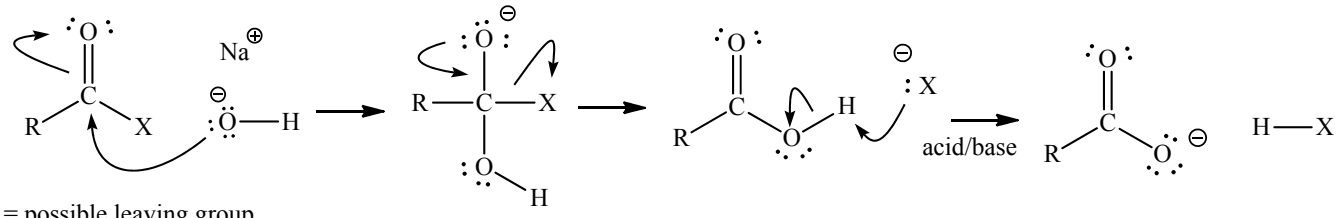
carboxylates are good nucleophiles at methyl, primary, secondary, allyl and benzyl RX, making esters, only E2 at tertiary RX

S_N2 with acetate produces esters, then **acyl substitution** with hydroxide produces the alcohol, if desired. A new type of substitution reaction.

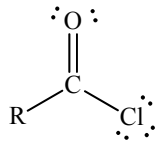


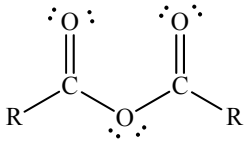
Look at similarities to imide hydrolysis, just below.

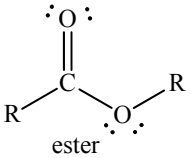
Problem 7 – Show the acyl substitution mechanism for each functional group with hydroxide.

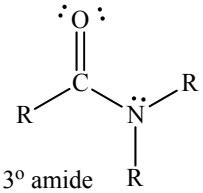


Functional Groups to use

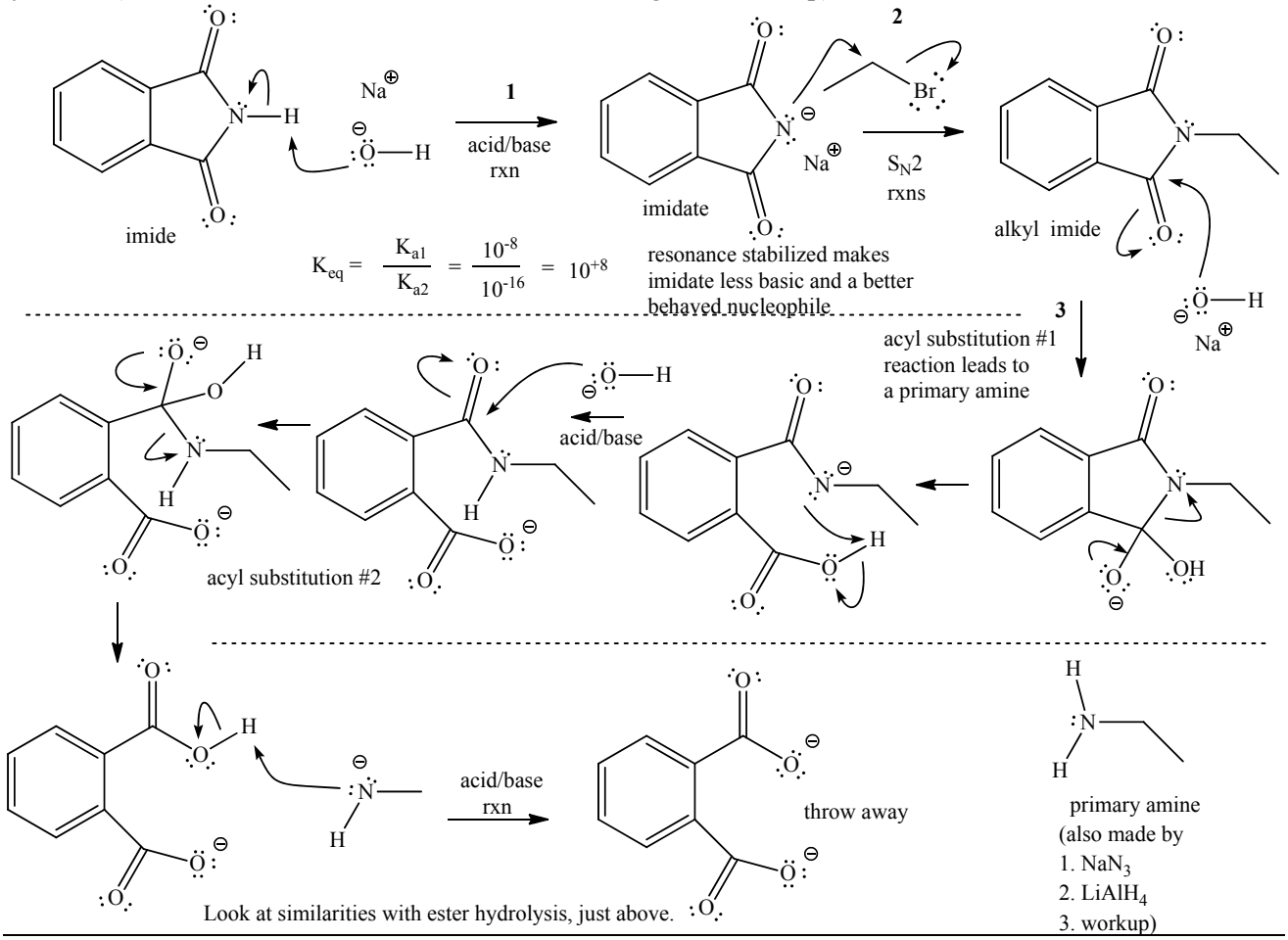




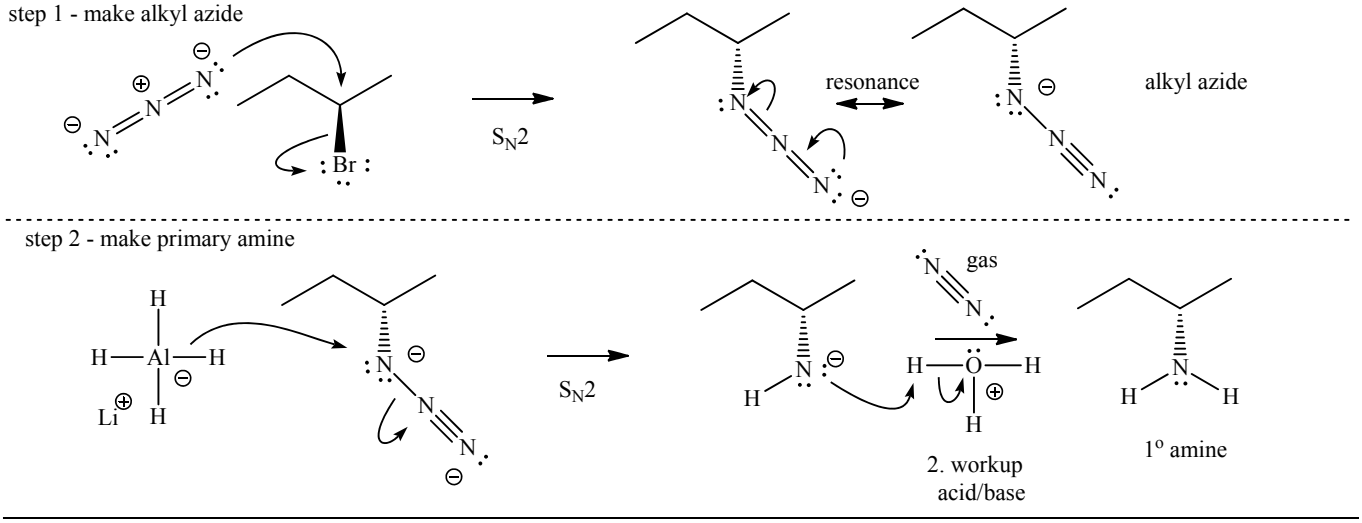




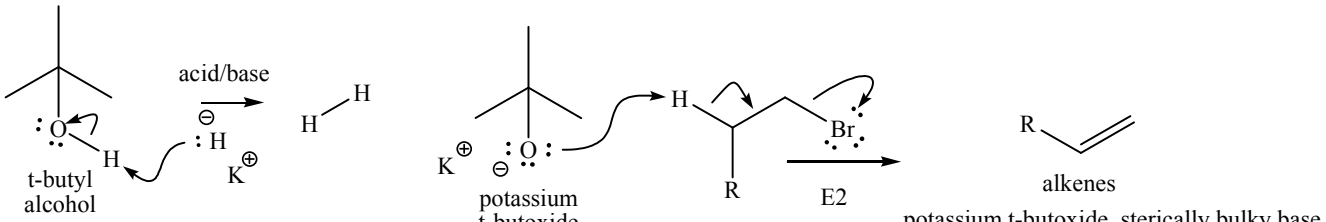
Make imidates and use as nucleophile at RX centers to convert to primary amines. 1. Make alkyl imides 2. Hydrolyze in base to make primary amines (acyl substitution) 3. Workup) = Gabriel amine synthesis; duplicates azide amine synthesis (1. S_N2 with NaN_3 2. S_N2 with $LiAlH_4$ at nitrogen 3. workup)



Alternative azide strategy to make primary amines (S_N2 and acid/base reactions)



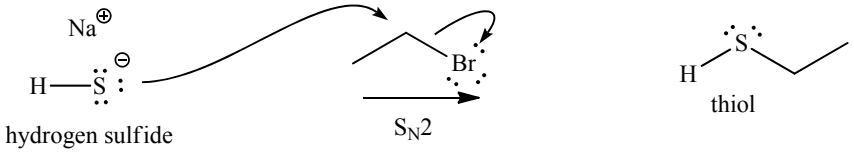
Make potassium t-butoxide and use as sterically large, strong base at 1° RCH_2-X, 2° R_2CH-X and 3° R_3C-X in E2 reactions.



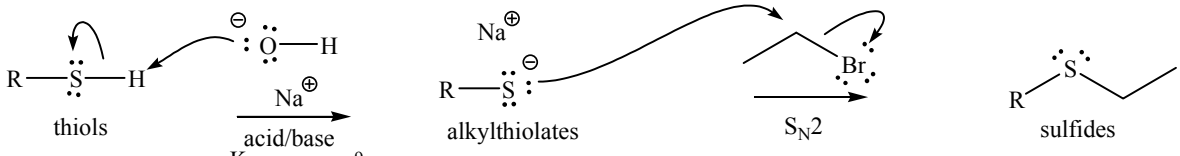
$K_{eq} = \frac{K_{a1}}{K_{a2}} = \frac{10^{-19}}{10^{-37}} = 10^{+18}$

potassium t-butoxide, sterically bulky base that mostly does E2 reactions with RX compounds (except S_N2 with CH_3-X).

Make thiols using NaSH as the nucleophile at Me-X, 1° RCH_2-X and 2° R_2CH-X in S_N2 reactions.

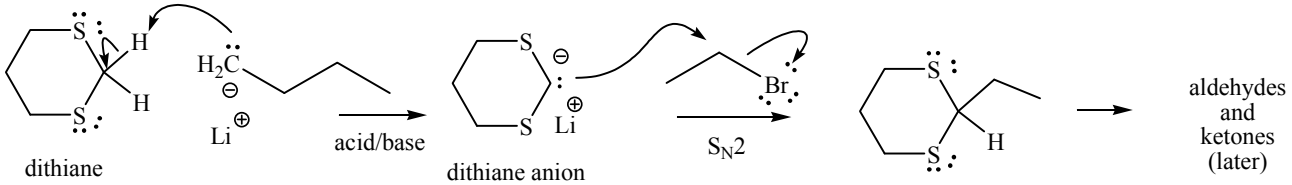


Make thiolates and use as nucleophiles at Me-X, 1° RCH_2-X and 2° R_2CH-X in S_N2 reactions.



$K_{eq} = \frac{K_{a1}}{K_{a2}} = \frac{10^{-9}}{10^{-16}} = 10^{+7}$

Synthesis of lithium dithiane anion (acid/base) 2. SN2 with RX 3. Hydrolyze to make aldehydes or ketones)

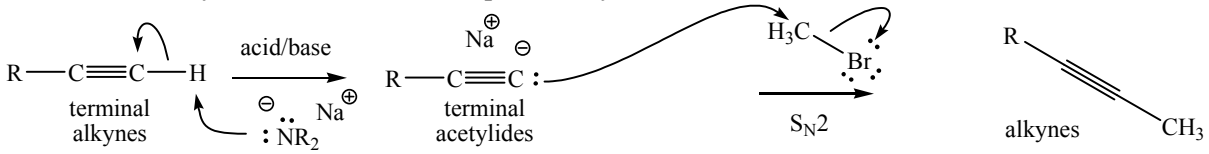


$K_{eq} = \frac{K_{a1}}{K_{a2}} = \frac{10^{-50}}{10^{-35}} = 10^{+15}$

A good nucleophile that can be made into aldehydes and ketones

---

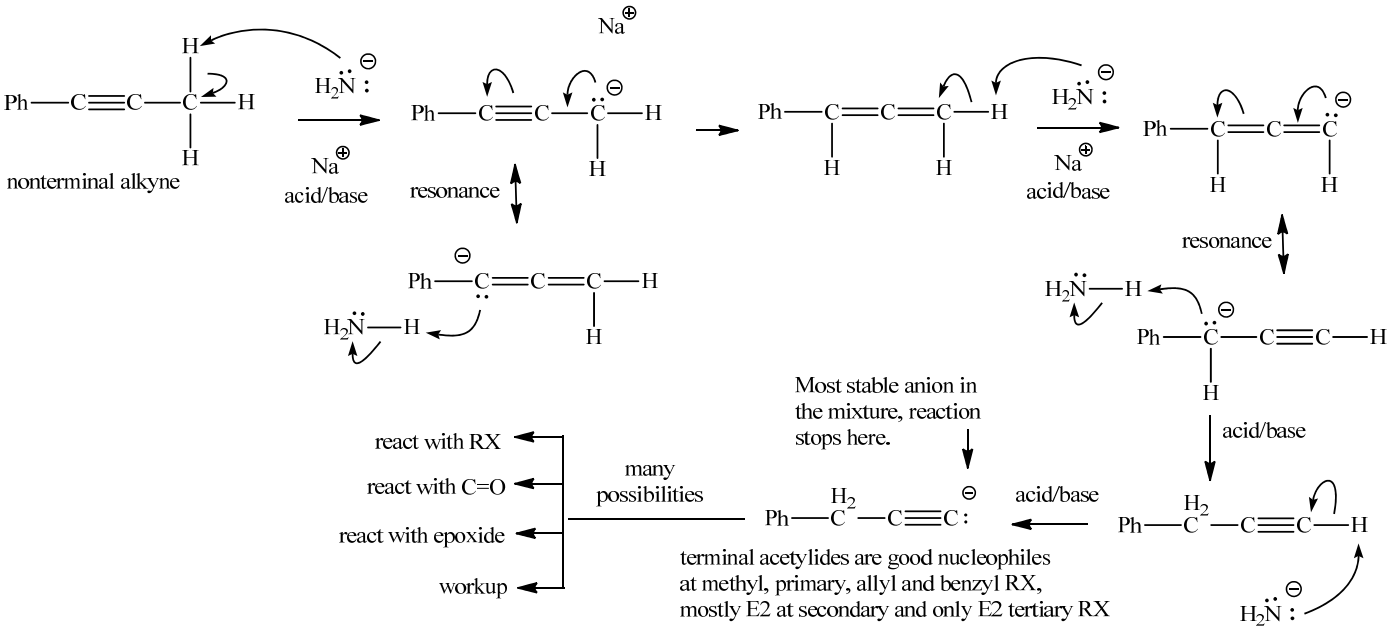
Make terminal acetylides and use as nucleophiles only at Me-X and 1° RCH_2-X in S_N2 reactions.



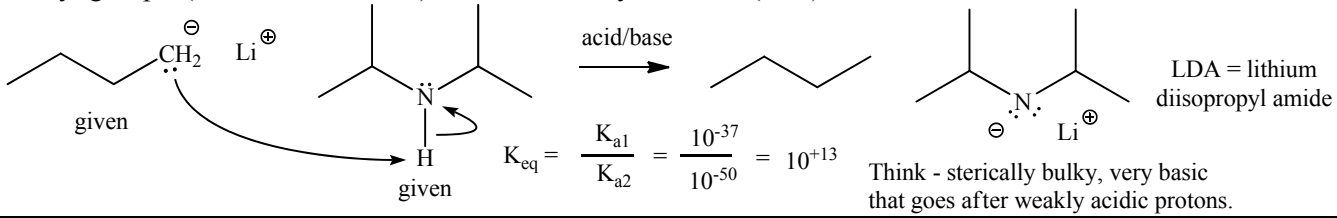
$K_{eq} = \frac{K_{a1}}{K_{a2}} = \frac{10^{-25}}{10^{-37}} = 10^{+12}$

terminal acetylides are good nucleophiles at methyl, primary, allyl and benzyl RX, but mostly E2 at secondary and only E2 tertiary RX

Zipper reaction – moves triple bond to end of linear chain to form the most stable anionic charge, further chemistry is possible. This reaction is almost identical to tautomers, without any heteroatoms.

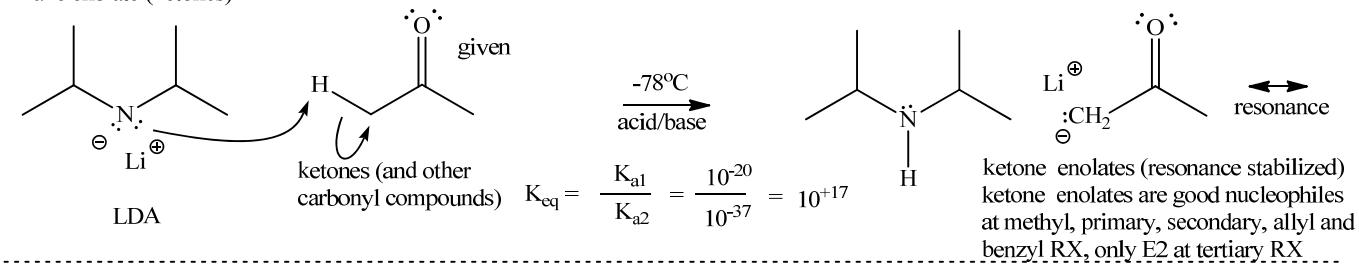


Synthesis of lithium diisopropyl amide, LDA, sterically bulky, very strong base used to remove C_α-H proton of carbonyl groups. (acid / base reaction) to make carbonyl enolates (next).

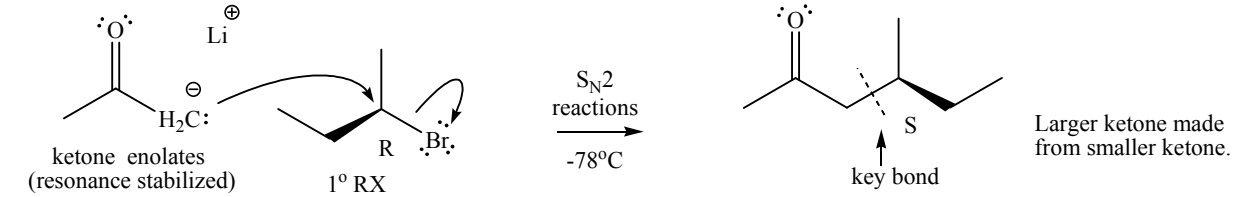


React ketone enolate (nucleophile) with R-Br electrophile (Me, 1° and 2° RX compounds)

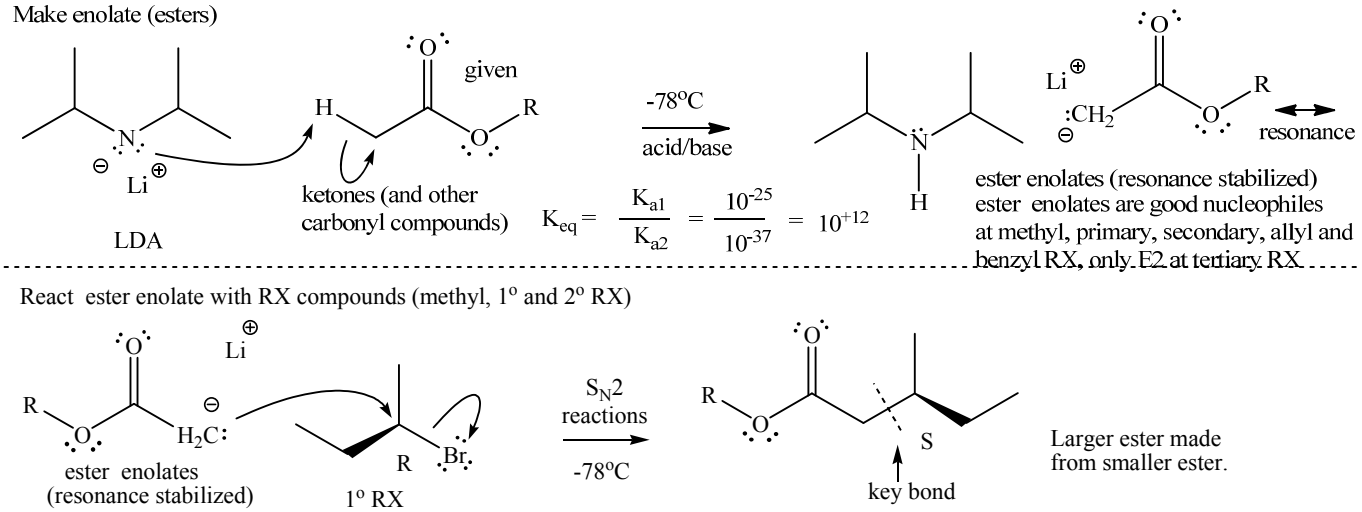
Make enolate (ketones)

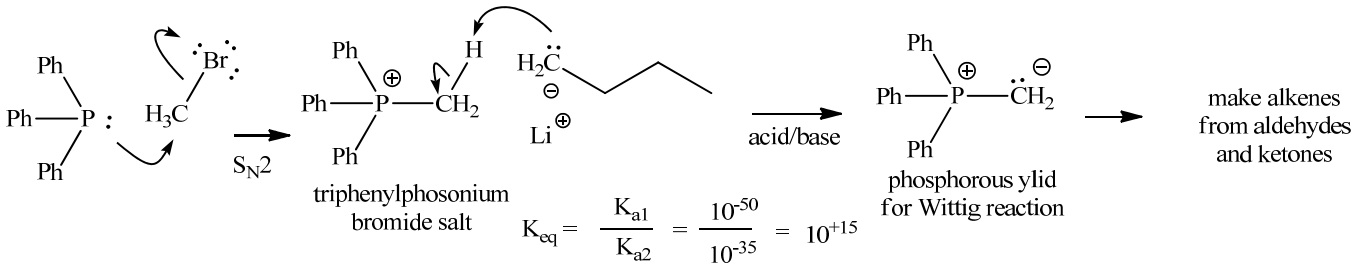


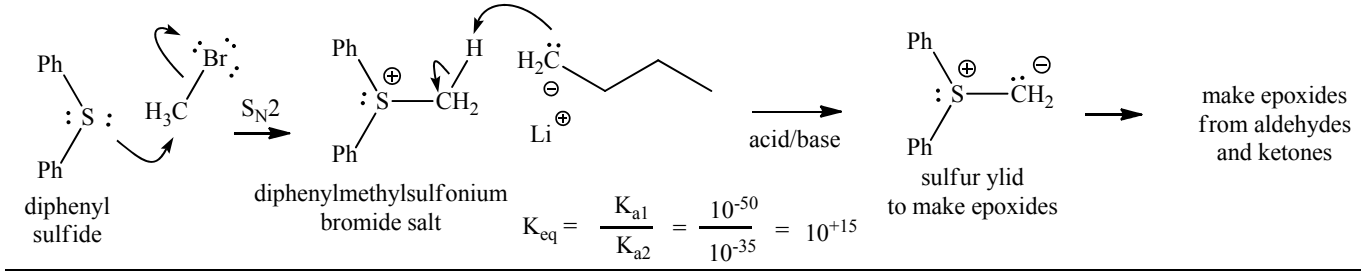
React ketone enolate with RX compounds (methyl, 1° and 2° RX)



React ester enolate (nucleophile) with R-Br electrophile (Me, 1° and 2° RX compounds)





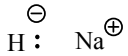


Clarification of "Hydride" electron pair donors: In our course sodium hydride and potassium hydride are always "basic," and lithium aluminum hydride and sodium borohydride are always nucleophilic hydride.

Basic hydride

In our course, sodium hydride (NaH) and potassium hydride (KH) are *always* basic (= electron pair donation by hydride to a proton), *never* a nucleophile. The conjugate acid of hydride is hydrogen gas (with a $pK_a = 37$, H_2 can hardly be considered an acid).

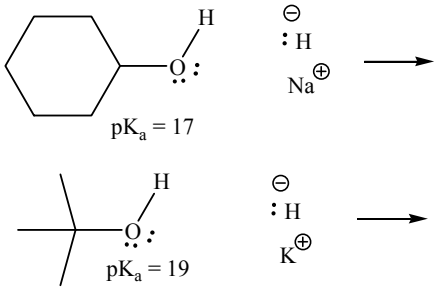
Sodium hydride and potassium hydride (KH)



Aldrich, 2012
$39 / 100 grams
60% oil dispersion
MW = 24.0 g/mol

Aldrich, 2012
$128 / 75 grams
30% oil dispersion
MW = 40.1 g/mol

Problem 8 – Write an arrow pushing mechanism for each of the following reactions.

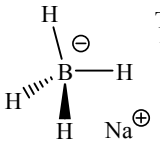


	pK_a
ROH	16-19
H-H	37

Nucleophilic hydride – Formation of C-H bonds using nucleophilic lithium aluminum hydride and sodium borohydride.

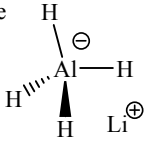
In our course, sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$ = LAH) are inorganic salts containing *nucleophilic hydride*, very unusual nucleophiles. Both reagents supply nucleophilic hydride that can displace X in S_N2-like reactions with RX compounds. Sodium borohydride and lithium aluminum hydride are used in many other reactions. They also react with carbonyl compounds (C=O) and epoxides (both to be discussed more later). We will often use the deuterium version of borohydride and aluminum hydride so we can identify where a reaction occurred. In reality, this is not very common because of the expense. But, for purposes of probing your understanding of S_N2 reactions, using them shows if you understand what is happening. The deuterium isotope of hydrogen reacts similarly to the proton isotope, but there are experimental methods which allow us to observe where a reaction took place (e.g. NMR).

Sodium borohydride and lithium aluminum hydride (LAH) - 4 equivalents of hydride per anion

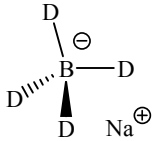


Aldrich, 2012
$312 / 100 grams
MW = 37.8 g/mol

The hydride salts are way more common.

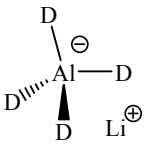


Aldrich, 2012
$120 / 100 grams
MW = 38 g/mol



Aldrich, 2012
$254 / 5 grams
MW = 41.8 g/mol

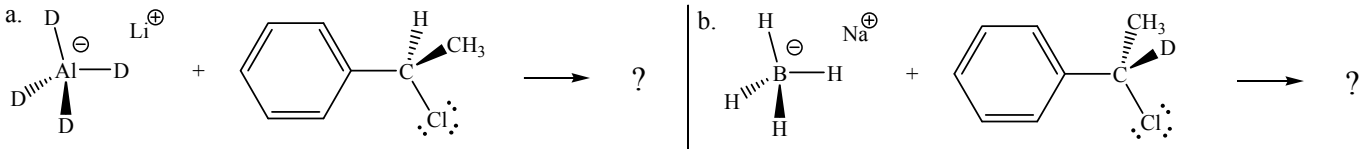
The deuteride salts are way more expensive.



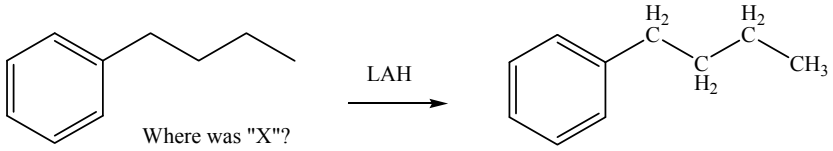
Aldrich, 2012
$125 / 5 grams
MW = 42 g/mol

All these reagents will undergo S_N2 reactions at RX centers. Because there is a greater difference in electronegativity between aluminum and hydrogen than boron and hydrogen, LAH is more reactive than sodium borohydride. This won't be important for us to know until we study carbonyl reactions.

Problem 9 – Write an arrow pushing mechanism for the following reaction.



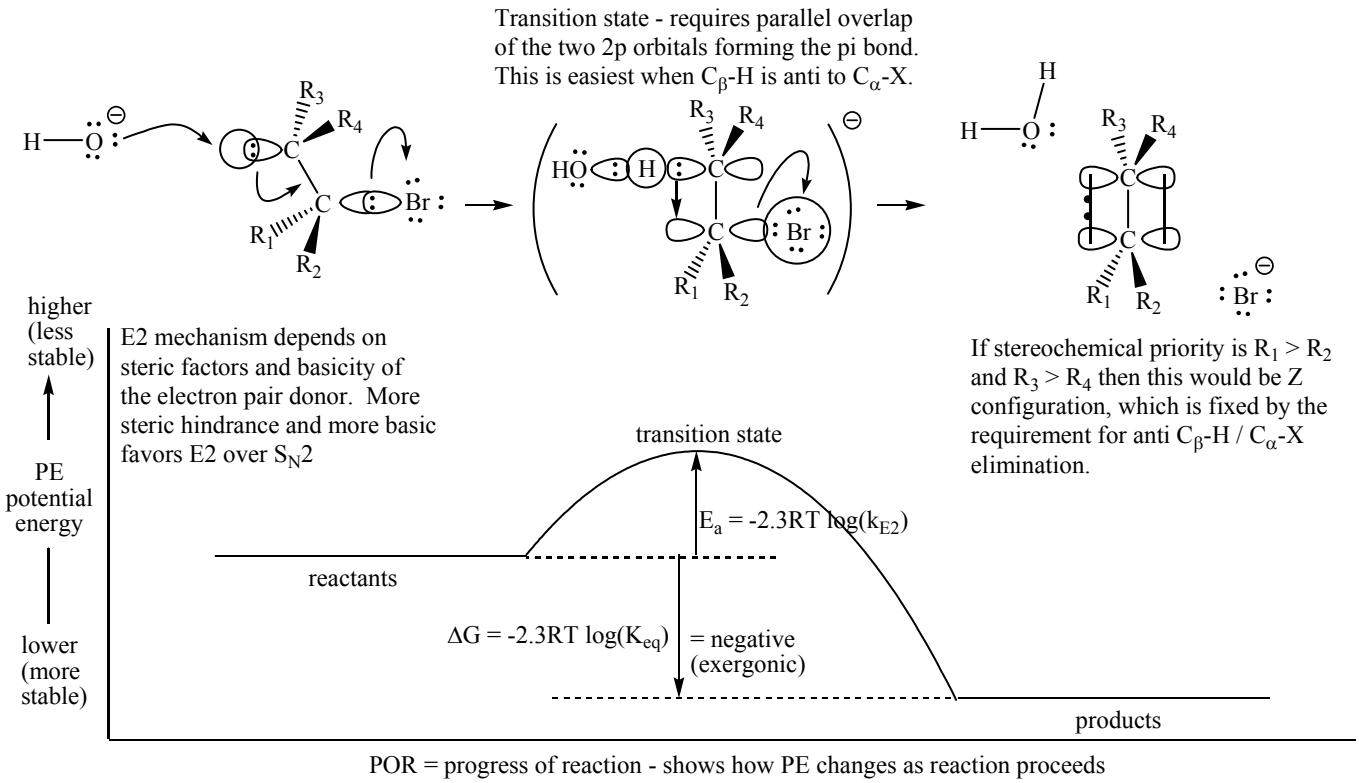
Problem 10 – It is hard to tell where the hydride was introduced since there are usually so many other hydrogens in organic molecules. Where could have X have been in the reactant molecule? There are no obvious clues. Which position(s) for X would likely be more reactive with the hydride reagent? Could we tell where X was if we used $LiAlD_4$?



E2 Reactions Compete with S_N2 Reactions

E2 reactions also occur at the backside relative to the leaving group, but at C_β-H instead of C_α-X. The C_β-H proton has to be anti to the C_α-X to allow for parallel overlap of the 2p orbitals that form the new pi bond. This allows elimination to occur in a concerted manner. The syn conformation also has parallel overlap of 2p orbitals, but is present in less than 1% due to an eclipsed conformation (staggered conformations > 99%).

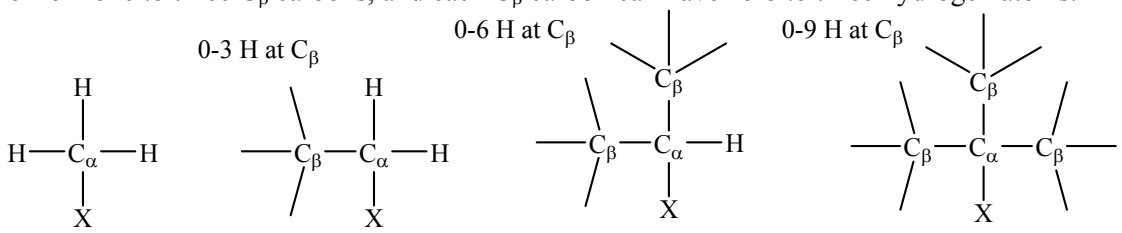
E2 Potential Energy vs. Progress of Reaction Diagram (= concerted, energy picture looks very similar to S_N2)



POR = progress of reaction - shows how PE changes as reaction proceeds

<u>Keeping Track of the C_β Hydrogens in E2 reactions</u>

At least one C_β position, with a hydrogen atom, is necessary for an E2 reaction to occur. In more complicated systems there may be several different types of hydrogen atoms on different C_β positions. In E2 reactions there can be anywhere from one to three C_β carbons, and each C_β carbon can have zero to three hydrogen atoms.



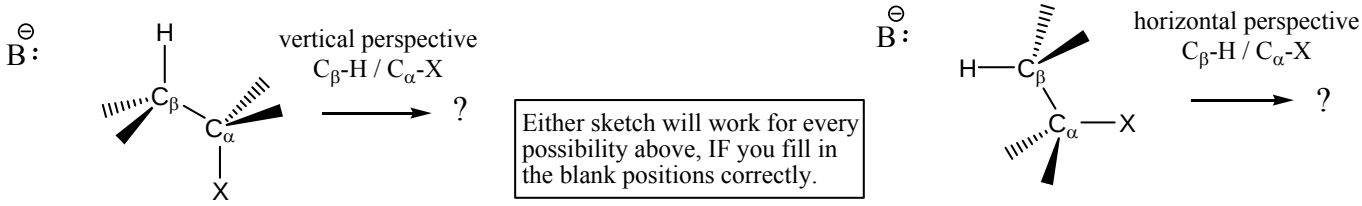
zero C_β positions
unique methyl,
only S_N2 possible

one C_β position
1° RX, usually S_N2 > E2
(except with t-butoxide)

two C_β positions
(2° RX, S_N2 / E2
both competitive)

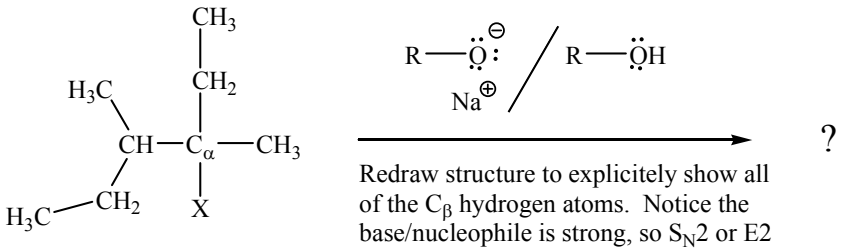
three C_β positions
(3° RX, only E2)

With proper rotations, each C_β-H may potentially be able to assume an anti conformation necessary for an E2 reaction to occur. There are a lot of details to keep track of and you must be systematic in your approach to consider all possibilities. Using one of these two perspectives may help your analysis of E2 reactions Let's consider a moderately complicated example (next problem).

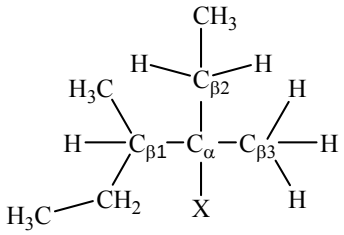


Either sketch will work for every possibility above, IF you fill in the blank positions correctly.

Problem 11 - How many total hydrogen atoms are on C_β carbons in the given RX compound? How many different types of hydrogen atoms are on C_β carbons (a little tricky)? How many different products are possible? Hint - Be careful of the simple CH_2. The two hydrogen atoms appear equivalent, but E/Z (cis/trans) possibilities are often present. (See below for relative expected amounts of the E2 products.)



Redraw structure to explicitely show all of the C_β hydrogen atoms. Notice the base/nucleophile is strong, so S_N2 or E2 reaction are considered. The RX pattern is tertiary, so no S_N2 is possible. There are three C_β carbon atoms and all of them have hydrogen atoms on them. That leaves E2 reaction as the only possible choice.

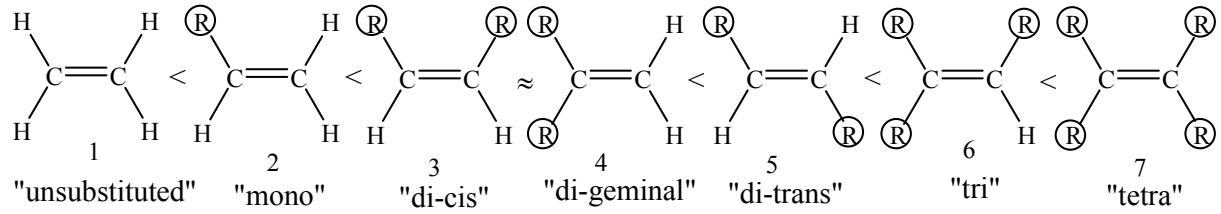


There are two chiral centers, C_α and $C_{\beta1}$, that make this structure more complicated than we are treating it. Possible stereoisomers are RR, RS, SR and SS.

Stability of pi bonds

In elimination reactions, more substituted alkenes are normally formed in greater amounts. Greater substitution of carbon groups in place of hydrogen atoms at alkene carbons (and alkyne carbon atoms too) translates into greater stability (lower potential energy). Alkene substitution patterns are shown below. There are three types of disubstituted alkenes and their relative stabilities are usually as follows: geminal ≈ cis < trans.

Relative stabilities of substitued alkenes.



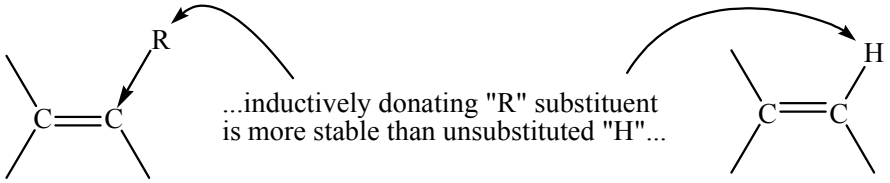
The more substituted alkenes are usually more stable than less substitued alkenes. Substitution here, means an Ⓡ group for a hydrogen atom at one of the four bonding positions of the alkene.

1 = unsubstituted alkene (ethene is unique)
2 = monosubstituted alkene
3 = cis disubstituted alkene
4 = geminal disubstituted alkene
5 = trans disubstituted alkene
6 = trisubstituted alkene
7 = tetrasubstituted alkene

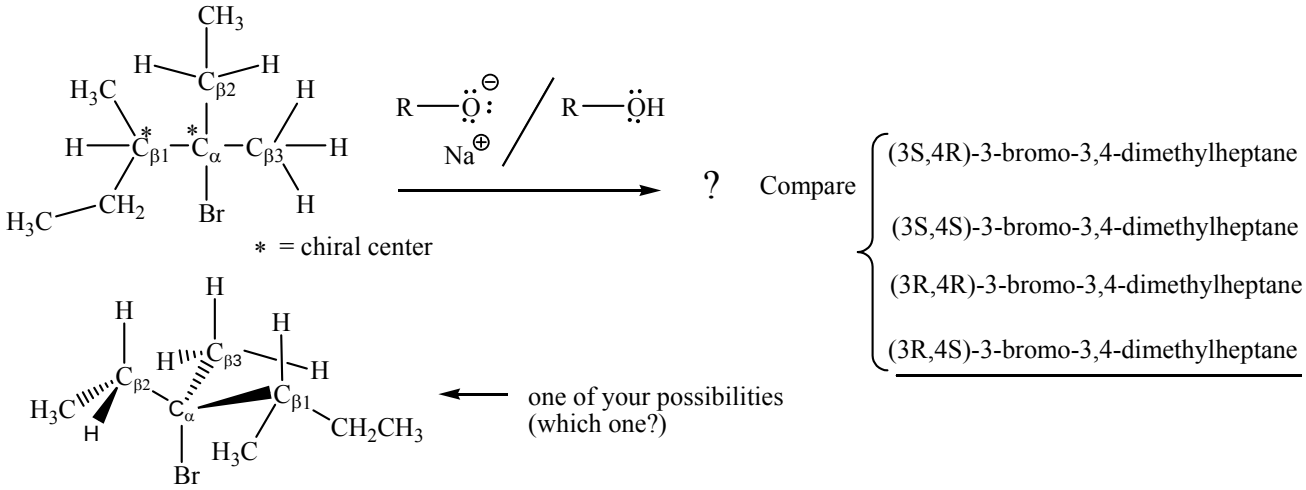
Saytzeff's rule: More stable alkenes tend to form faster (because of lower E_a) in dehydrohalogenation reactions (E2 and E1). They tend to be the major alkene product, though typically a little of every alkene product possible is obtained.

Possible explanations for greater stability with greater substitution of the pi bond

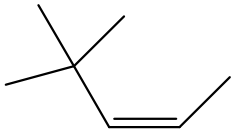
A fairly simple-minded explanation (the one we will use) for the relative alkene stabilities is provided by considering the greater electronegativity of an sp^2 orbital over an sp^3 orbital. An alkyl group (R→) inductively donates electron density better than a simple hydrogen. From the point of view of a more electronegative sp^2 alkene carbon, it is better to be connected to an electron donating alkyl carbon group than a simple hydrogen atom. The more R groups at the four sp^2 positions of a double bond, the better. However, be aware that other features, such as steric effects or resonance effects, can reverse expected orders of stability.



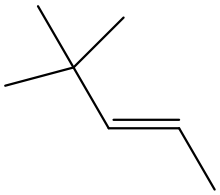
Problem 12 - Reconsider the elimination products expected in problem 1 and identify the ones that you now expect to be the major and minor products. How would an absolute configuration of C_α as R, compare to C_α as S? What about $C_{\beta 1}$ as R versus S?



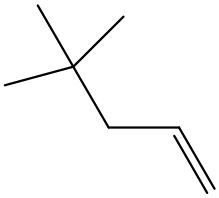
Problem 13 -Provide an explanation for any unexpected deviations from our general rule for alkene stabilities above. A more negative potential energy is more stable.



ΔH^o_f = -18.7 kcal/mole

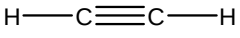


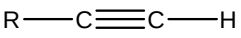
ΔH^o_f = -22.7 kcal/mole

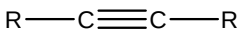


ΔH^o_f = -19.97 kcal/mole

Problem 14 – Order the stabilities of the alkynes below (1 = most stable). Provide a possible explanation.

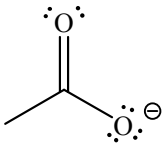
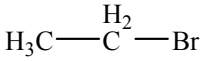
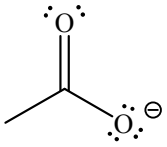
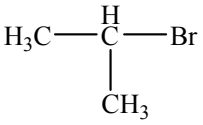
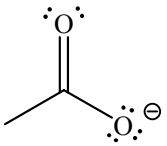
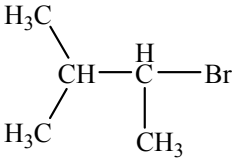
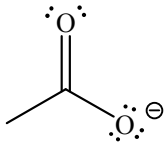
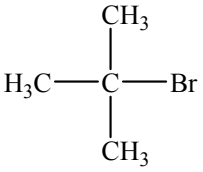




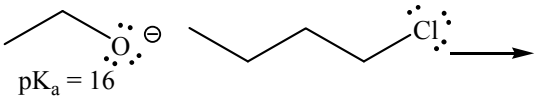


"R" = a simple alkyl group

Problem 15 - Propose an explanation for the following table of data. Write out the expected products and state by which mechanism they formed. Nu: ¨ /B: ¨ = CH_3CO_2 ¨ (a weak base, but good nucleophile).

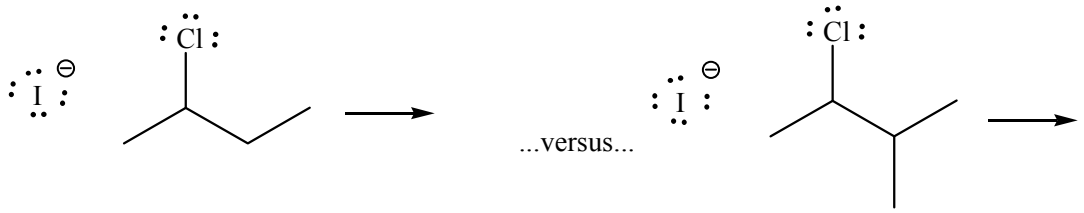
		percent substitution	percent elimination	our rules
		100 %	0 %	$S_N2 > E2$
		100 %	0 %	$S_N2 > E2$
		11 %	89 %	$S_N2 > E2$ (wrong prediction)
		0 %	100 %	only E2

Problem 16 – One of the following reactions produces over 90% S_N2 product and one of them produces about 85% E2 product in contrast to our general rules (ambiguity is organic chemistry's middle name). Match these results with the correct reaction and explain why they are different.

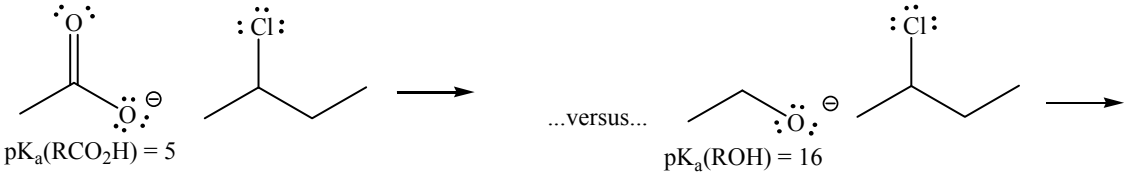


Problem 17 - A stronger base (as measured by a higher pK_a of its conjugate acid) tends to produce more relative amounts of E2 compared to S_N2, relative to a second (weaker) base/nucleophile. Greater substitution at C_α and C_β also increases the proportion of E2 product, because the greater steric hindrance slows down the competing S_N2 reaction. Use this information to make predictions about which set of conditions in each part would produce relatively more elimination product. Briefly, explain your reasoning. Write out all expected <u>elimination</u> products. Are there any examples below where one reaction (S_N2 or E2) would completely dominate?

a.

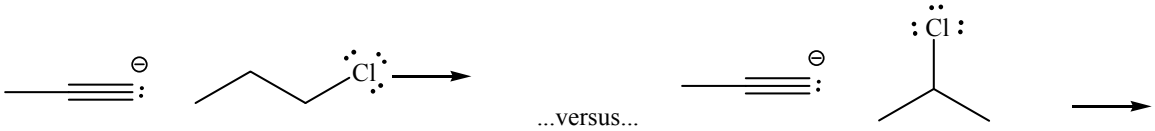


b.

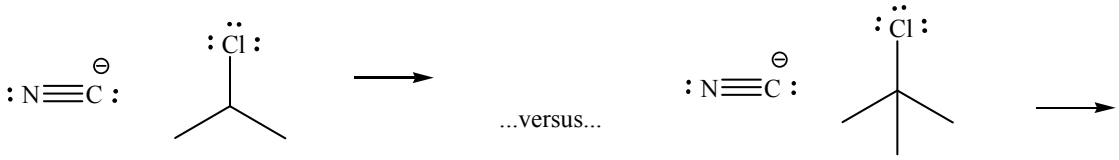


$pK_a(RCO_2H) = 5$ $pK_a(ROH) = 16$

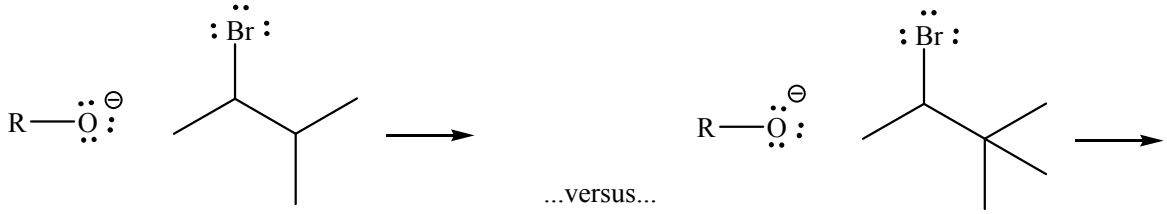
c.



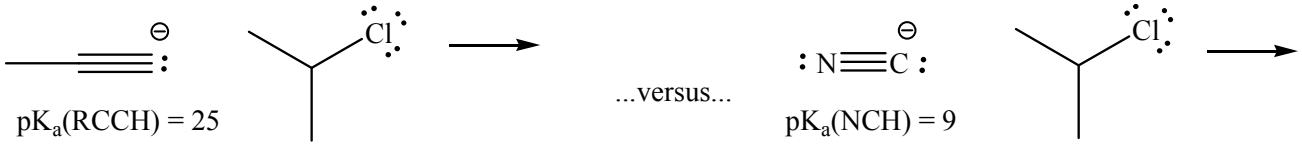
d.



e.

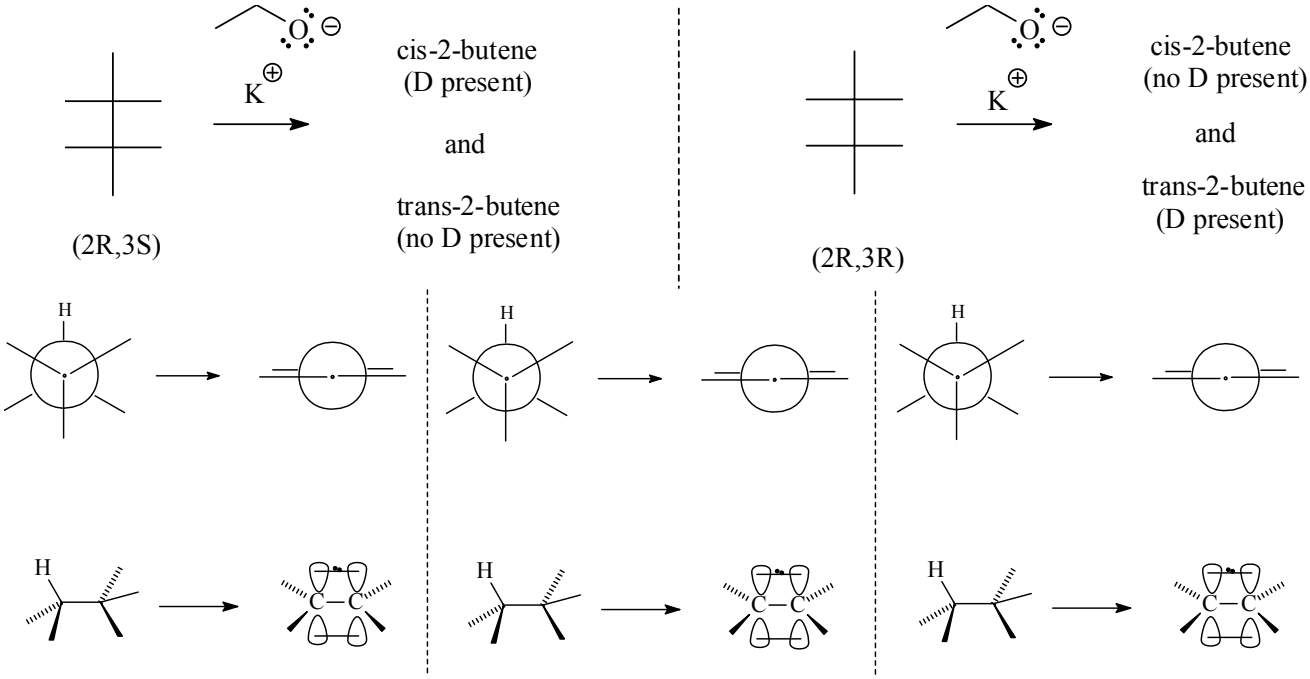


f.

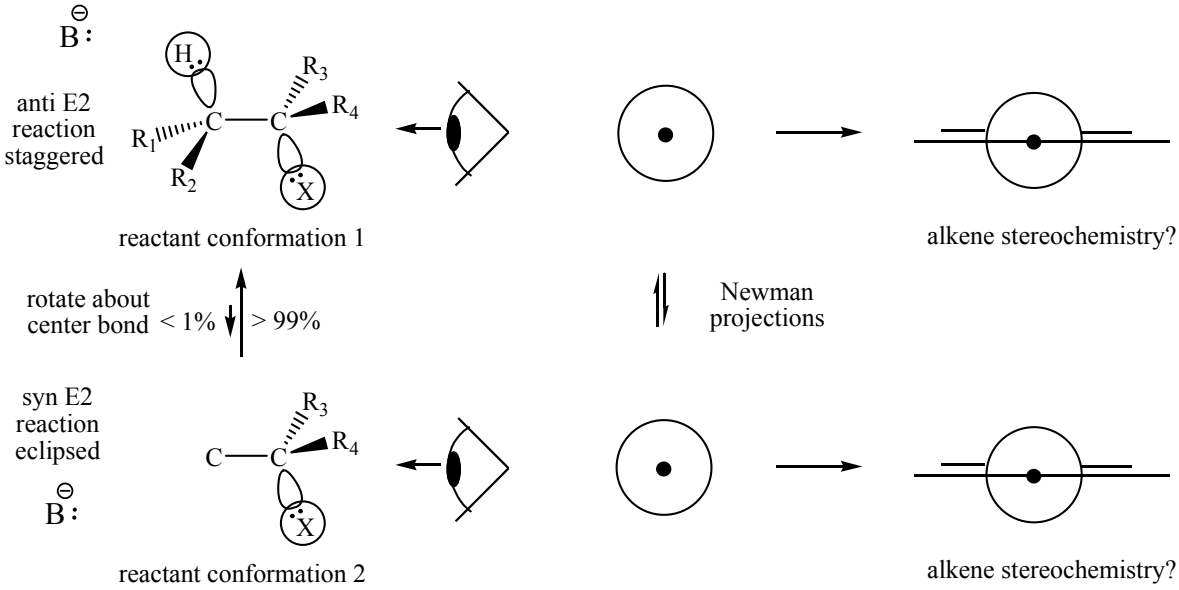


$pK_a(RCCH) = 25$ $pK_a(NCH) = 9$

Problem 18 - (2R,3S)-2-bromo-3-deuteriobutane when reacted with potassium ethoxide produces cis-2-butene having deuterium and trans-2-butene not having deuterium. The diastereomer (2R,3R)-2-bromo-3-deuteriobutane under the same conditions produces cis-2-butene not having deuterium and trans-2-butene having deuterium present. Explain these observations by drawing the correct 3D structures, rotating to the proper conformation for elimination and showing an arrow pushing mechanism leading to the observed products. (Protium = H and deuterium = D; H and D are isotopes. Their chemistries are similar, but we can tell them apart.)



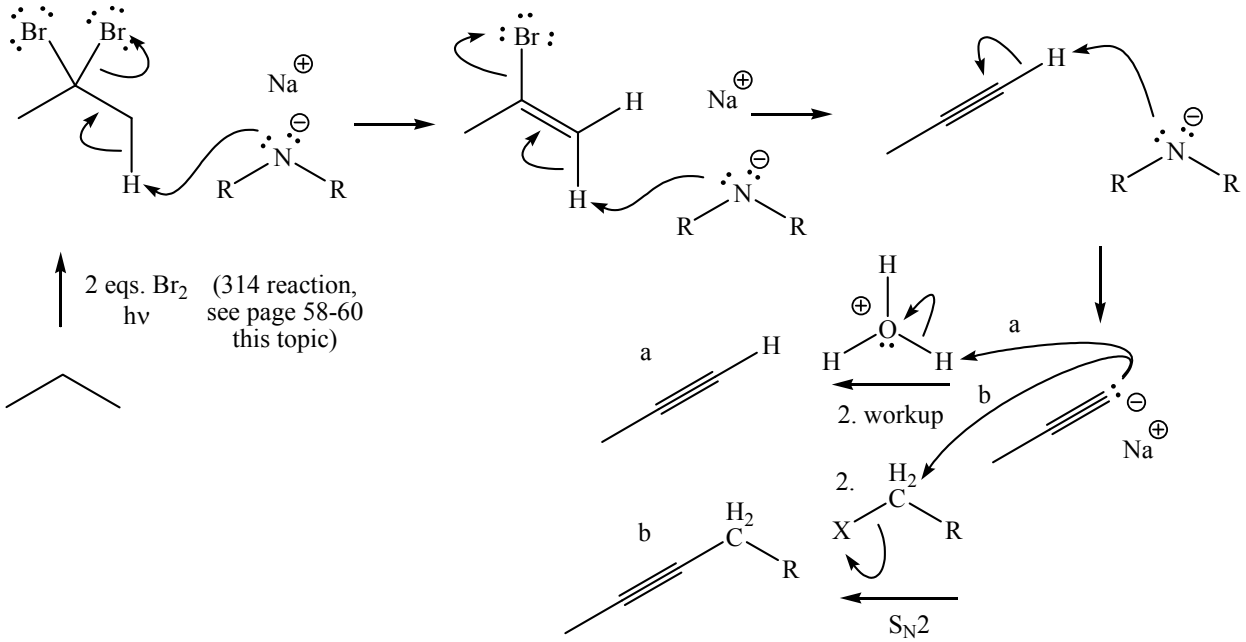
Problem 19 - Draw a Newman projection of the two possible conformations leading to E2 reaction. Show how the orientation of the substituents about the newly formed alkene compares.



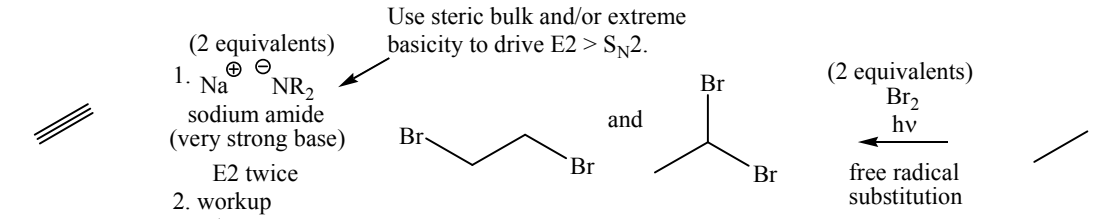
Alkyne synthesis (via two E2 reactions with RBr_2 and $NaNR_2$, two times)

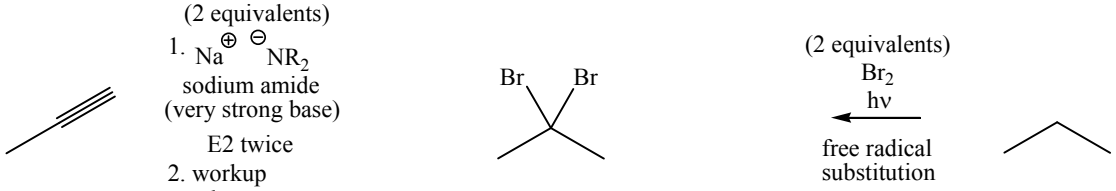
Sample alkynes using double E2 reactions of 1. RBr_2 + $NaNR_2$ 2. Workup (neutralize mixture)

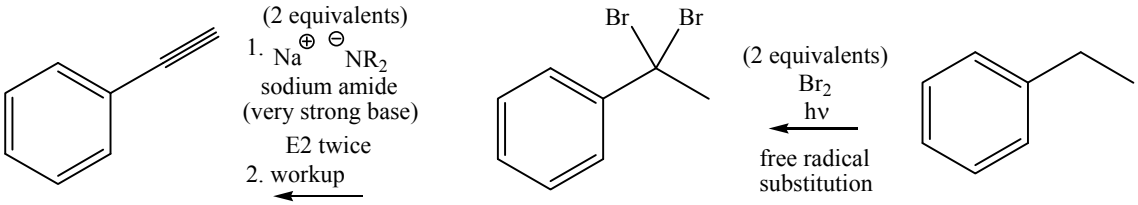
Possible steps in mechanism (E2 twice then 2. acid/base or 2. RX electrophile)



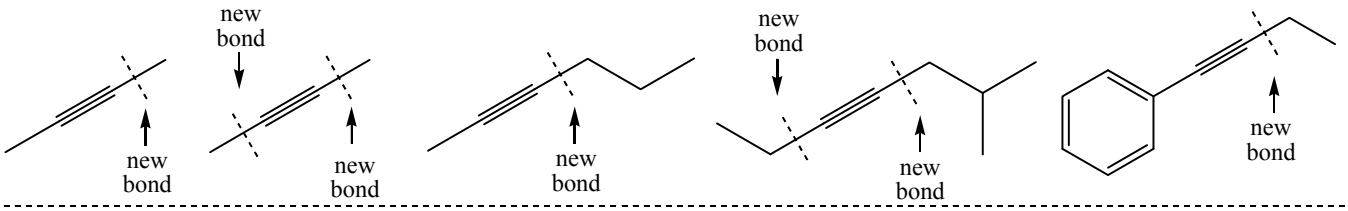
Make starting alkynes using two leaving groups and very basic R_2N^- starting from an alkane.

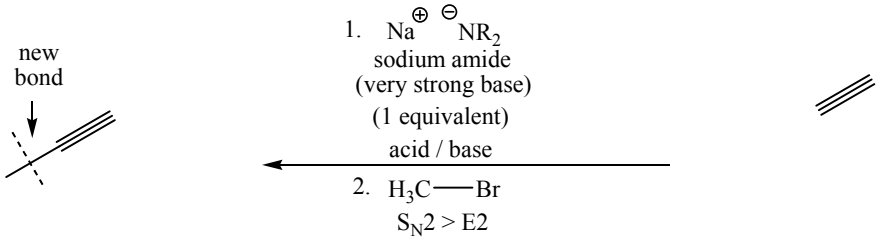


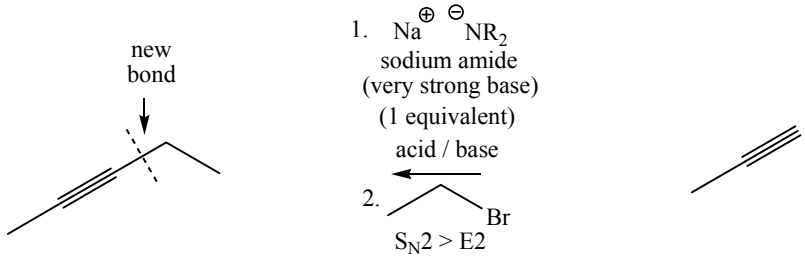




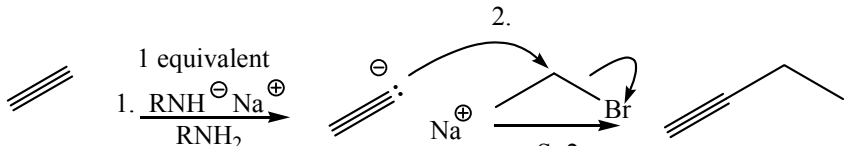
Sample alkynes using S_N2 reactions of 1. Terminal alkyne + $NaNR_2$ 2. S_N2 only at methyl or primary R-X (can do this twice starting with ethyne)



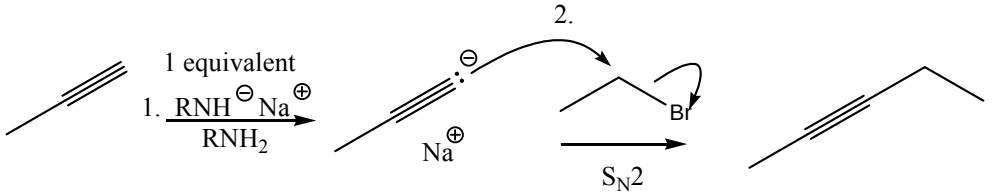




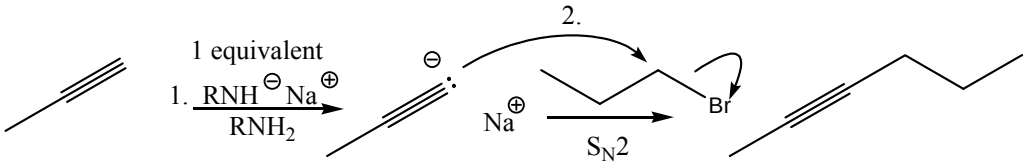
Terminal acetylides are OK nucleophiles at methyl and 1° RX, but E2 > S_N2 at 2° RX and only E2 at 3° RX.



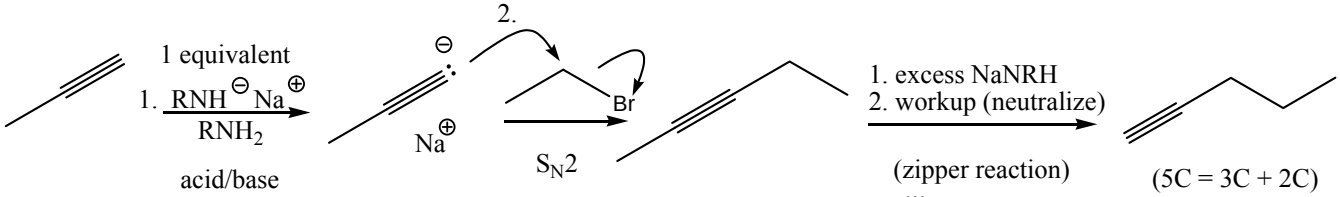
(4C = 2C + 2C)
terminal alkyne



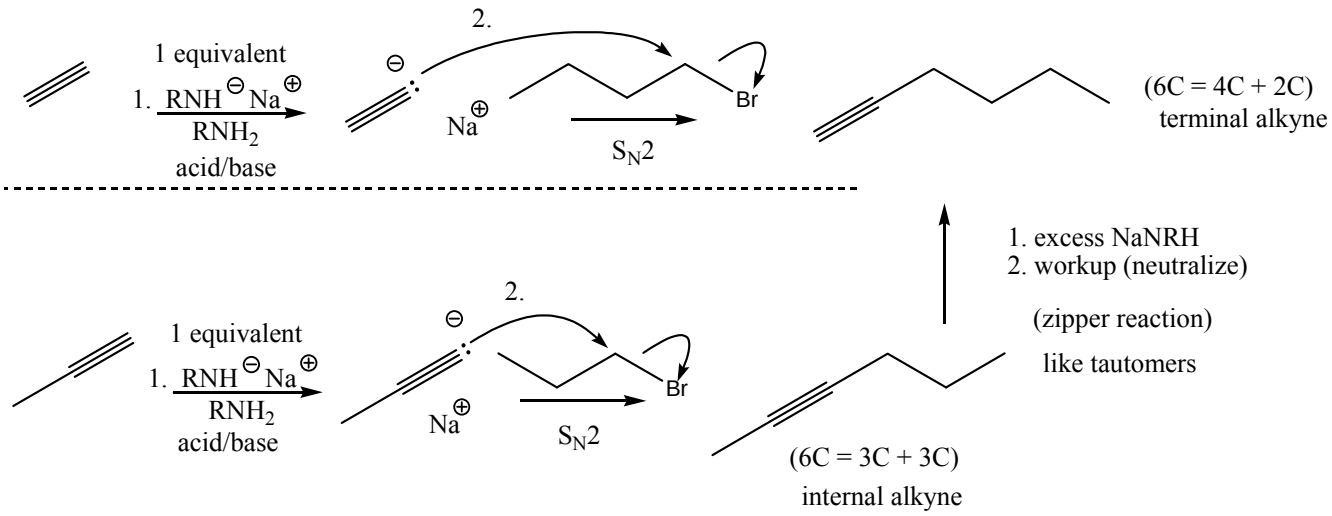
(5C = 3C + 2C)
internal alkyne



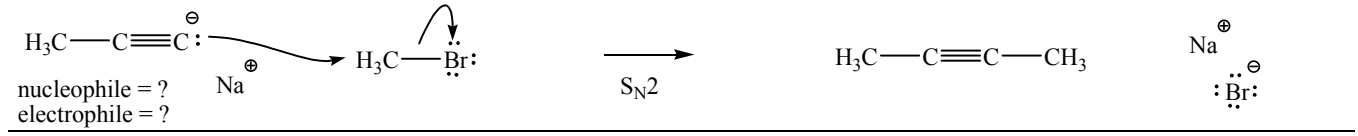
(6C = 3C + 3C)
terminal alkyne



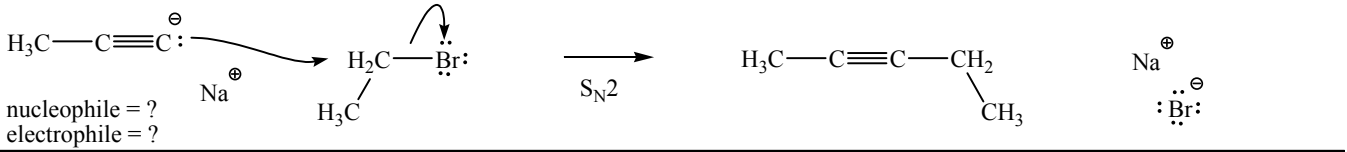
(5C = 3C + 2C)
internal alkyne



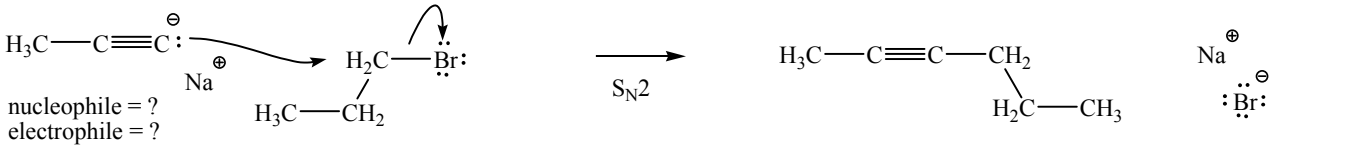
terminal acetylides (S_N2 only at methyl RX and 1° RX) → larger alkynes



nucleophile = ?
electrophile = ?

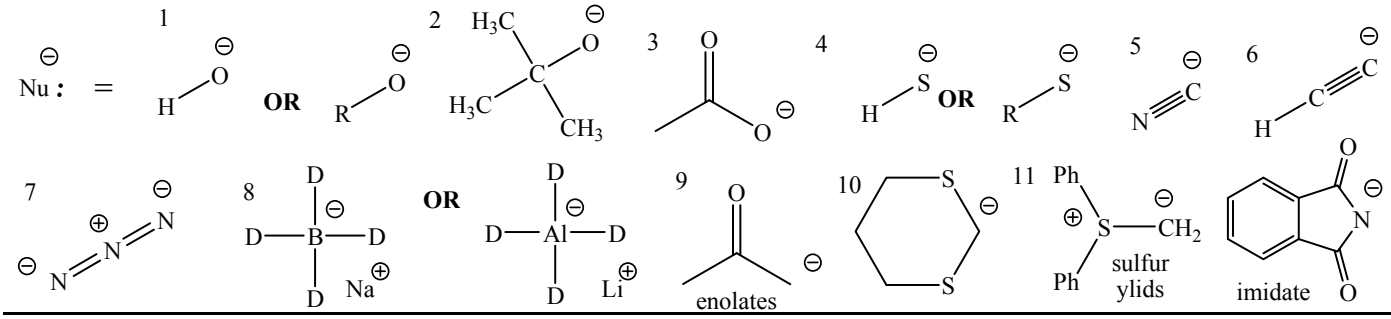


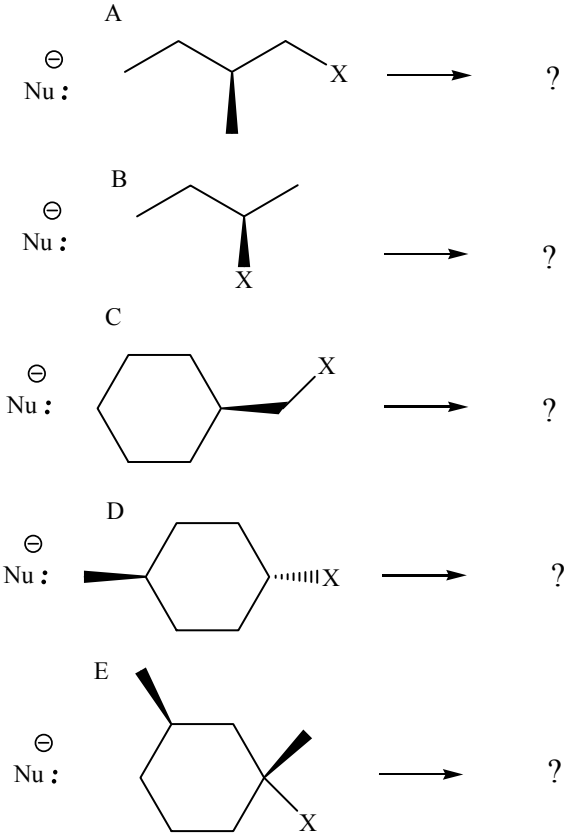
nucleophile = ?
electrophile = ?



nucleophile = ?
electrophile = ?

Problem 20 – What are the possible products of the following reactions? What is the major product(s) and what is the minor product(s)? There are 55 possible combinations.





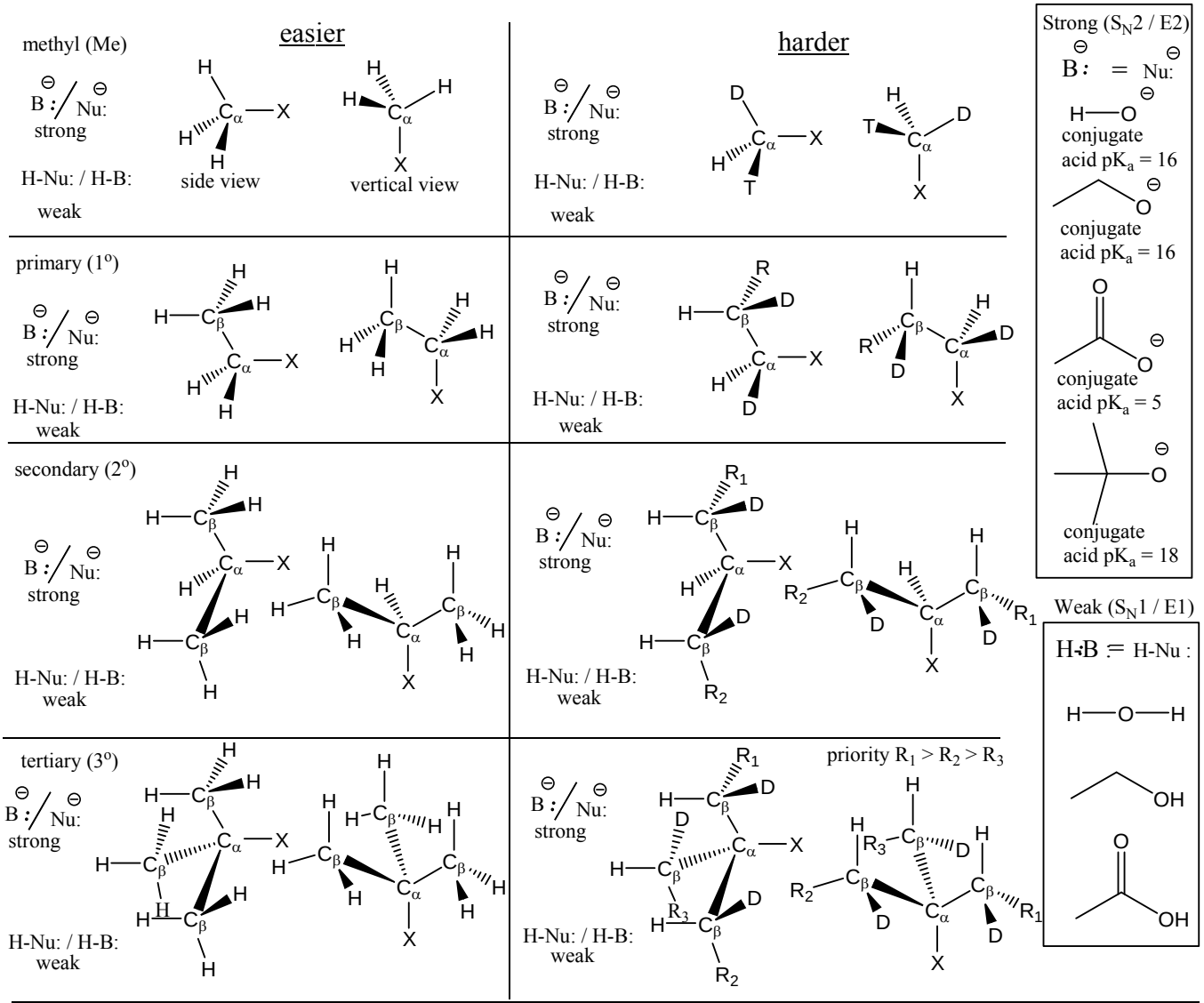
X = $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$ ...a good leaving group

Reaction Templates - sideways and vertical perspectives (either one will work)

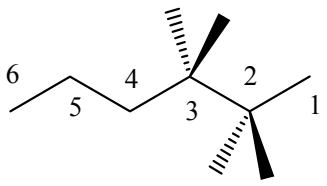
S_N2/E2 (Nu:$^{\ominus}$ / B:$^{\ominus}$) always backside for S_N2 and usually anti C_α-H/C_β-X attack for E2

S_N1/E1 (H-Nu: / H-B:) - attack from either face of R^+ for both reactions (S_N1 and E1)

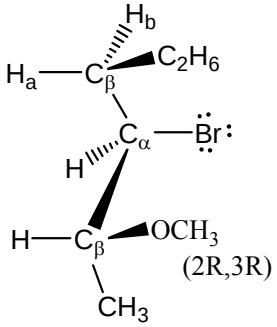
iotopes of hydrogen
H = protium (proton)
D = deuterium
T = tritium



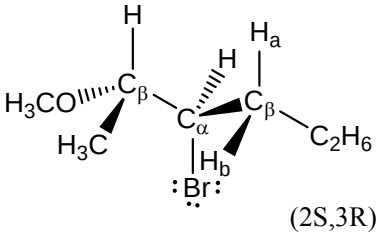
Example: 3-bromo-2-methoxyhexane (R,R), (S,S), (R,S), (S,R)



template

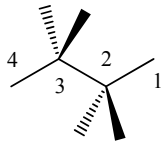


vertical view



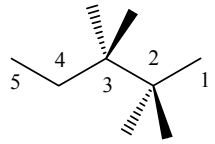
side view

Examples - you can use the vertical views or side views presented above. (Never ending supply of problems.)

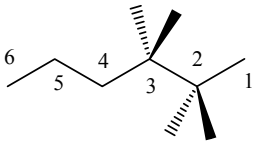


2-bromo-3-deuteriobutane
(R,R)
(S,S)
(R,S)
(S,R)

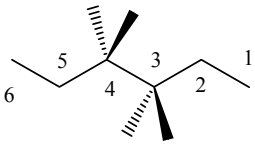
2-bromo-3-methylbutane
(R or S)



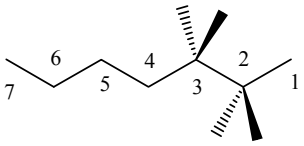
2-bromo-3-deuteriopentane	3-bromo-2-deuteriopentane	2-bromo-3-methylpentane	3-bromo-2-methylpentane
(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R or S)



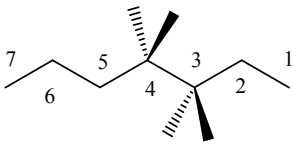
2-bromo-3-deuteriohexane	3-bromo-2-deuteriohexane	2-bromo-3-methylhexane	3-bromo-2-methylhexane
(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R or S)



3-bromo-4-deuteriohexane	3-bromo-4-methylhexane
(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)

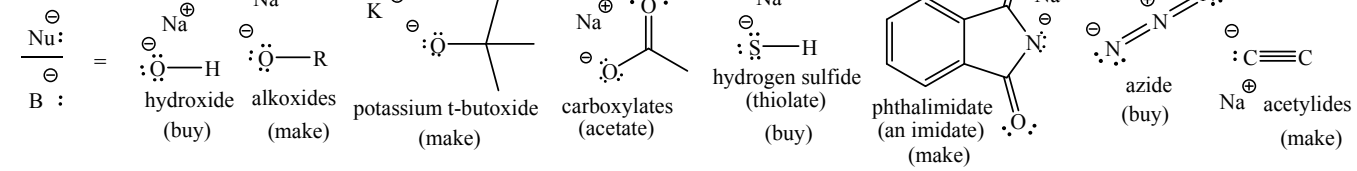


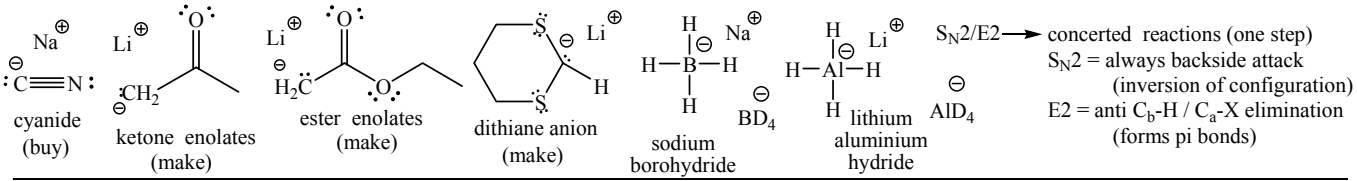
2-bromo-3-deuterioheptane	3-bromo-2-deuterioheptane	2-bromo-3-methylheptane	3-bromo-2-methylheptane
(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R or S)



3-bromo-4-deuterioheptane	4-bromo-3-deuterioheptane	3-bromo-4-methylheptane	4-bromo-3-methylheptane
(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)	(R,R) (S,S) (R,S) (S,R)

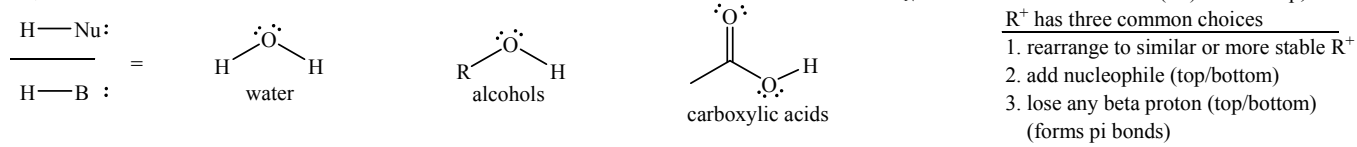
S_N2 / E2





$S_N2/E2$ → concerted reactions (one step)
S_N2 = always backside attack
(inversion of configuration)
E2 = anti C_b-H / C_a-X elimination
(forms pi bonds)

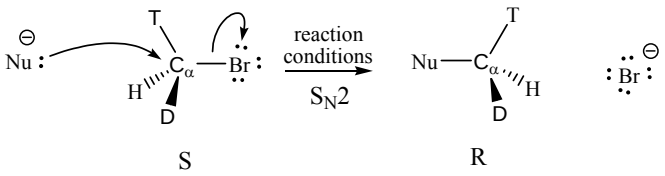
S_N1 / E1



$S_N1/E1$ → form carbocation (R^+) in first step,
R^+ has three common choices
1. rearrange to similar or more stable R^+
2. add nucleophile (top/bottom)
3. lose any beta proton (top/bottom)
(forms pi bonds)

Strong base/nucleophile conditions (negative charge in our course) leads to S_N2 and/or E2 reactions. Simple mechanisms.

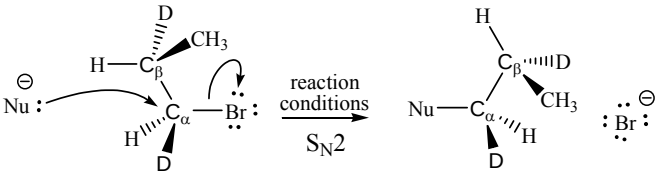
methyl pattern



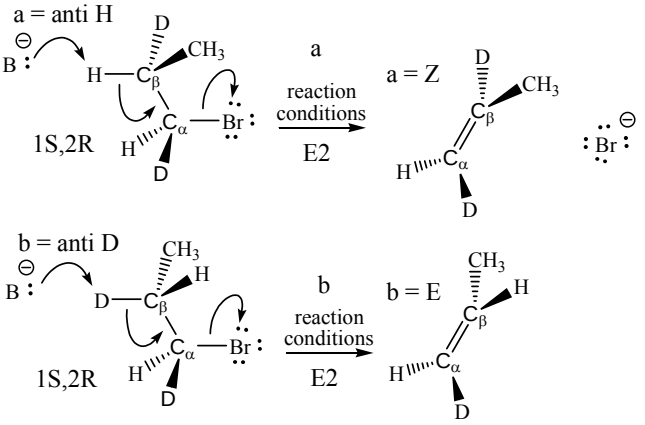
S R

There is no E2 at methyl RX

primary pattern (S_N2 > E2, except t-butoxide and $R_2N^{\ominus}$)

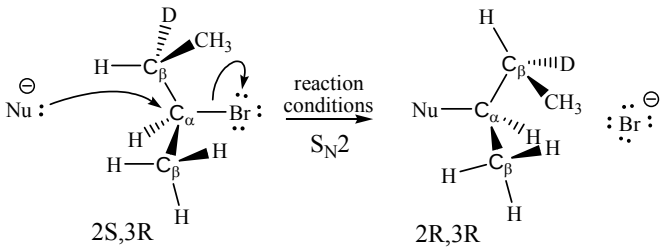


1S,2R 1R,2R

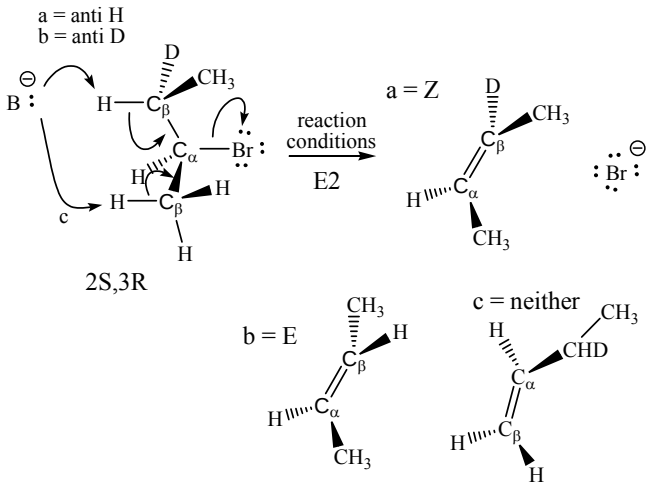


$E2 > S_N2$ when t-butoxide and $R_2N^{\ominus}$

secondary pattern
(S_N2 > E2, except $HO^{\ominus}$, $RO^{\ominus}$, $R_2N^{\ominus}$ and $RCC^{\ominus}$)



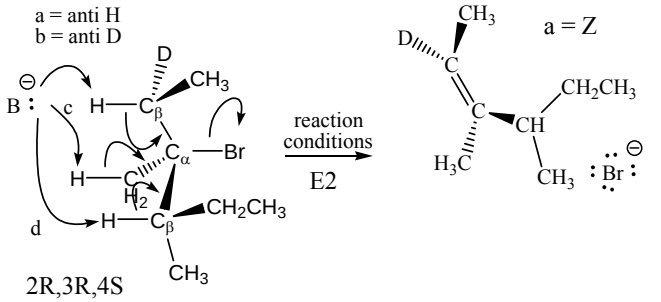
2S,3R 2R,3R



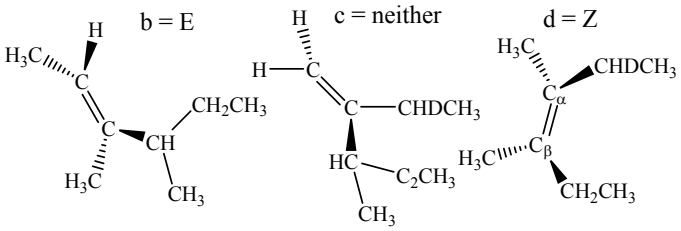
2S,3R

tertiary pattern

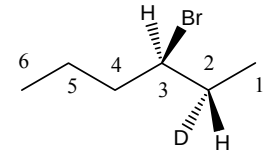
There is no S_N2 at tertiary RX



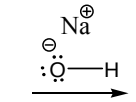
2R,3R,4S



Example Mechanisms shown below.



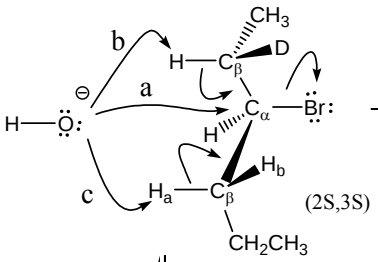
3R-bromo-2S-deuteriohexane



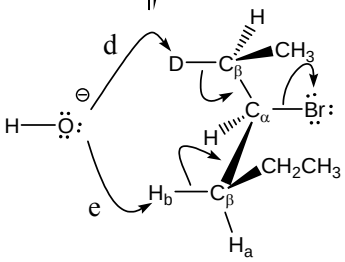
secondary RX (2^o)

One S_N2 product and four E2 products.

1. strong Nu:$^{\ominus}$ /B:$^{\ominus}$
2. 2^o R-X

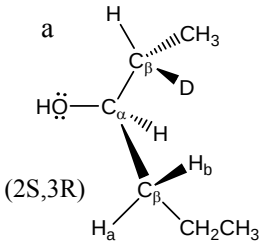


sigma bond rotations

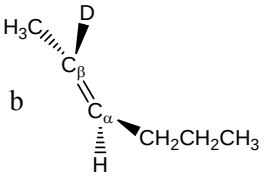


a, b, c

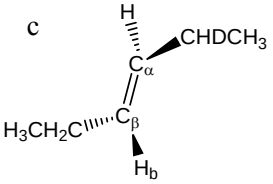
d, e



only one S_N2 product

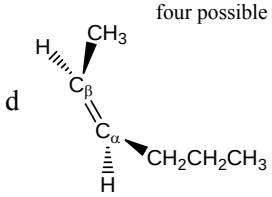


(2E, with "D")

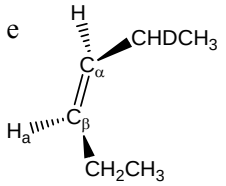


(3E, lost H_a)

four possible E2 products

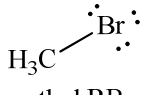
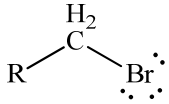
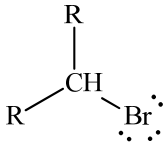
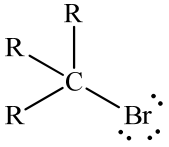
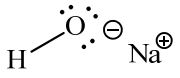
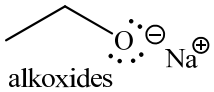
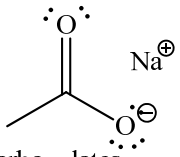
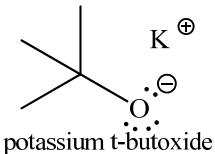
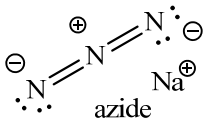
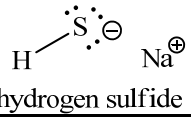
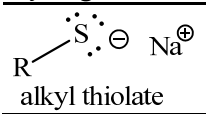
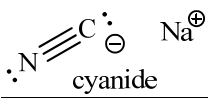
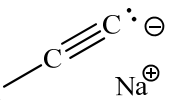
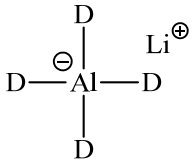


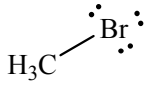
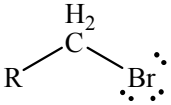
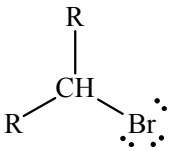
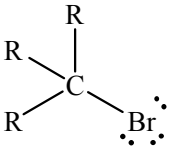
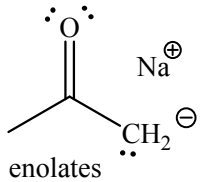
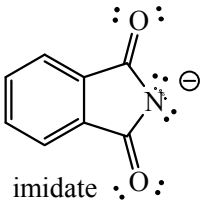
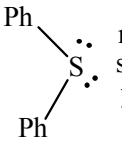
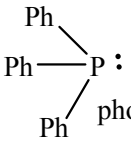
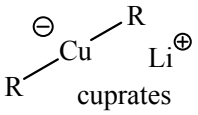
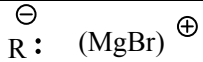
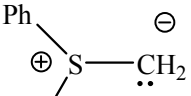
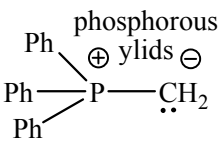
(2Z, without "D")



(3Z, lost H_b)

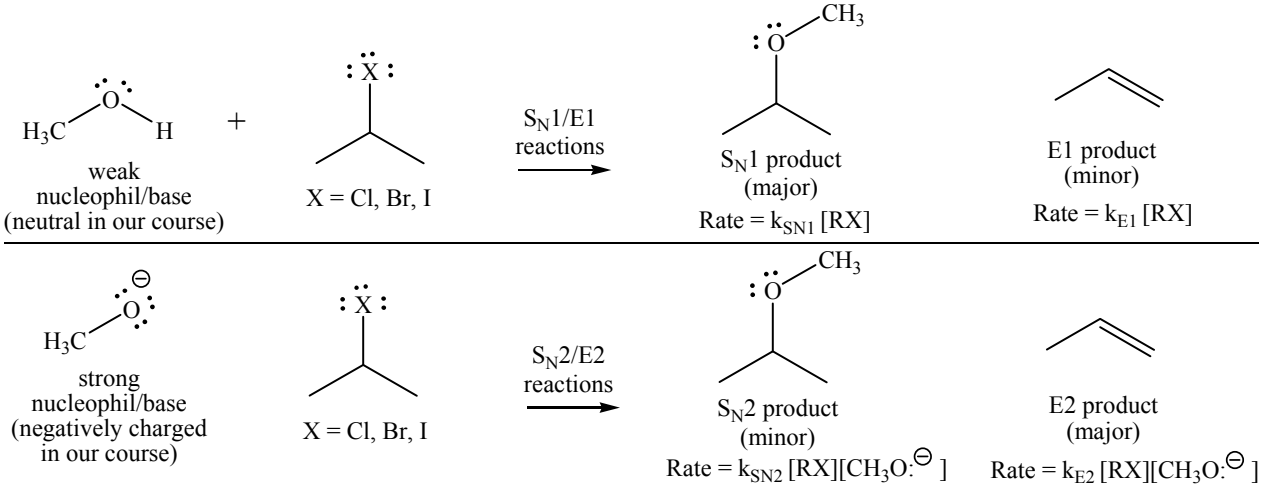
Important acid/base reactions are shown on pages 15-19. When necessary for a preliminary step of a reaction, you should consult those pages. Some of the strong base/nucleophiles used in our course are listed below along with the usual preferred reactions according to our simplistic rules. Cuprates will be discussed later. Missing are enolates, imidates, magnesium and lithium organometallics and a few others.

R-Br compounds / strong base/nucleophiles	 methyl RBr	 primary RBr	 secondary RBr	 tertiary RBr
 hydroxide	only S_N2 no C_β-H	S_N2 > E2	E2 > S_N2 too basic	only E2 too sterically hindered
 alkoxides	only S_N2 no C_β-H	S_N2 > E2	E2 > S_N2 too basic	only E2 too sterically hindered
 carboxylates	only S_N2 no C_β-H	S_N2 > E2	S_N2 > E2	only E2 too sterically hindered
 potassium t-butoxide	only S_N2 no C_β-H	E2 > S_N2 too basic and sterically hindered	E2 > S_N2 too basic and sterically hindered	only E2 too sterically hindered
 azide	only S_N2 no C_β-H	S_N2 > E2	S_N2 > E2	only E2 too sterically hindered
 hydrogen sulfide	only S_N2 no C_β-H	S_N2 > E2	S_N2 > E2	only E2 too sterically hindered
 alkyl thiolate	only S_N2 no C_β-H	S_N2 > E2	S_N2 > E2	only E2 too sterically hindered
 cyanide	only S_N2 no C_β-H	S_N2 > E2	S_N2 > E2	only E2 too sterically hindered
 terminal acetylides	only S_N2 no C_β-H	S_N2 > E2	E2 > S_N2 too basic	only E2 too sterically hindered
 lithium aluminium deuteride (hydride)	only S_N2 no C_β-H	S_N2 > E2	S_N2 > E2	not discussed in our course

R-Br compounds / strong base/nucleophiles	 methyl RBr	 primary RBr	 secondary RBr	 tertiary RBr
 enolates	only S_N2 no C_β-H	$S_N2 > E2$	$S_N2 > E2$	only E2 too sterically hindered
 imidate	only S_N2 no C_β-H	$S_N2 > E2$	$S_N2 > E2$	only E2 too sterically hindered
 make sulfur ylids	only S_N2 no C_β-H	$S_N2 > E2$	$S_N2 > E2$	only E2 too sterically hindered
 make phosphorous ylids	only S_N2 no C_β-H	$S_N2 > E2$	$S_N2 > E2$	only E2 too sterically hindered
 cuprates (covered in later topic)	only S_N2 no C_β-H	$S_N2 > E2$	$S_N2 > E2$	only E2 too sterically hindered
 Grignard reagents (covered in later topic)	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones
 organolithium reagents (covered in later topic)	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones
 sulfur ylids (covered in later topic)	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones
 phosphorous ylids (covered in later topic)	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones	react with aldehydes and ketones

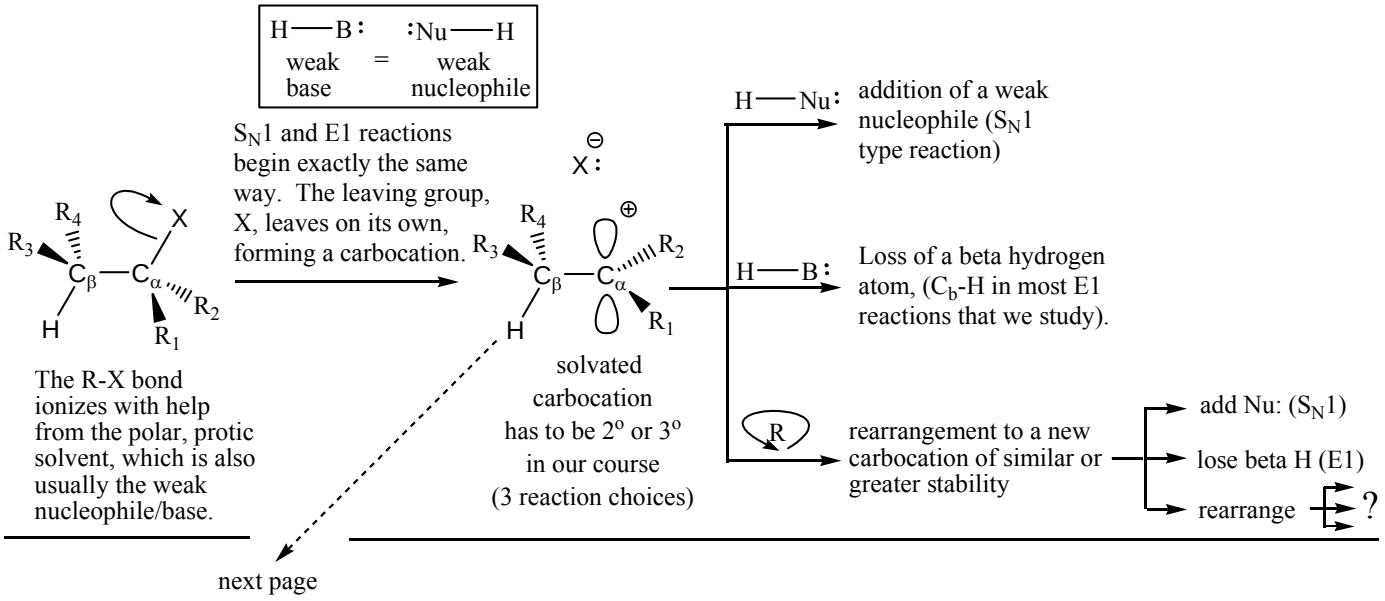
S_N1 and E1 Competition – Multistep Reactions Arising From Carbocation Chemistry

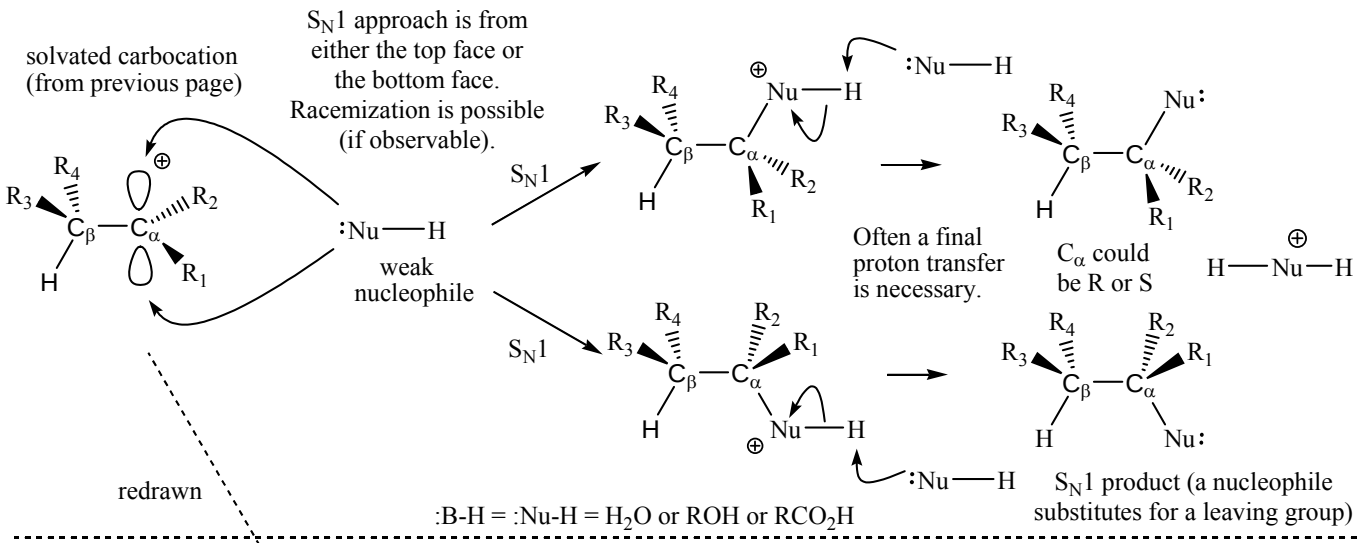
S_N2/E2 and S_N1/E1 reactions look very similar overall, but there are some key differences. In S_N2/E2 reactions the nucleophile/base is a strong electron pair donor (negative charge in our course), which is why they participate in the slow step of the reaction and force a concerted, one-step reaction. In S_N1/E1 reactions the nucleophile/base is a weak electron pair donor (stable, neutral molecules: H_2O, ROH and RCO_2H for us) and that's why they don't participate in the slow step of the reaction, which is ionization of the C_α-X bond. This leads to differences in reaction mechanisms, which show up in the rate law expression (kinetics is bimolecular = 2 or unimolecular = 1). The rate of "1" reactions only depends on how fast RX forms a carbocation. The unimolecular reactions lead to possible side reactions from carbocation rearrangements. You need to carefully look at the reaction conditions to decide what mechanisms are possible. You cut you choices in half when you decide that the electron pair donor is strong (negatively charged = S_N2/E2) or weak (neutral = S_N1/E1).

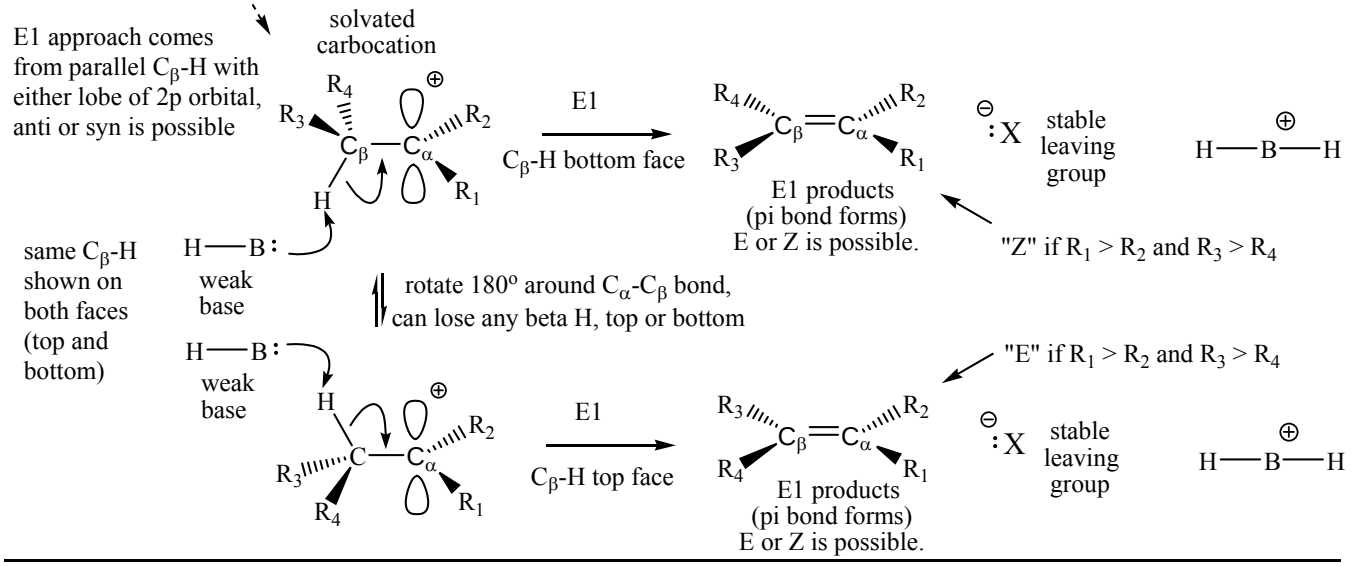


S_N1 and E1 reactions begin the same way, with ionization of the C_α-X bond to form a carbocation. Ion formation is energetically expensive. Protic solvents help by being able to solvate both cations and anions. Carbocations also need some help from inductive and/or resonance effects. If it can form, the initial carbocation intermediate typically follows one of three common paths: 1. addition of a weak nucleophile at carbon and/or 2. loss of a beta hydrogen to form a pi bond and/or 3. rearrangement to a similar or more stable carbocation. Rearrangement merely delays the ultimate reaction products: addition of a nucleophile or loss of a beta hydrogen atom to forma pi bond.

S_N1 and E1 reactions are multistep reactions. (H-Nu: / H-B: = H_2O, ROH, RCO_2H in our course)







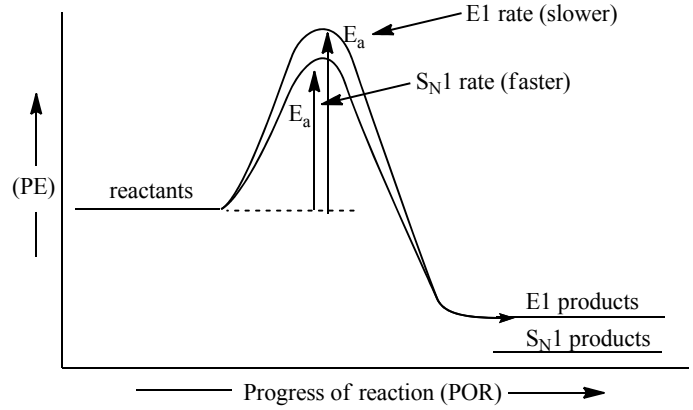
Terms

S = substitution E = elimination H-Nu: = weak nucleophile H-B: = weak base X = leaving group

1 = unimolecular kinetics (first order reaction, the rate in the slow step depends only on RX)

R-X = R-Cl, R-Br, R-I, R-OTs, ROH_2^+

:Nu—H = H—B: = usually a polar, protic solvent (or mixture) of H_2O, ROH or RCO_2H



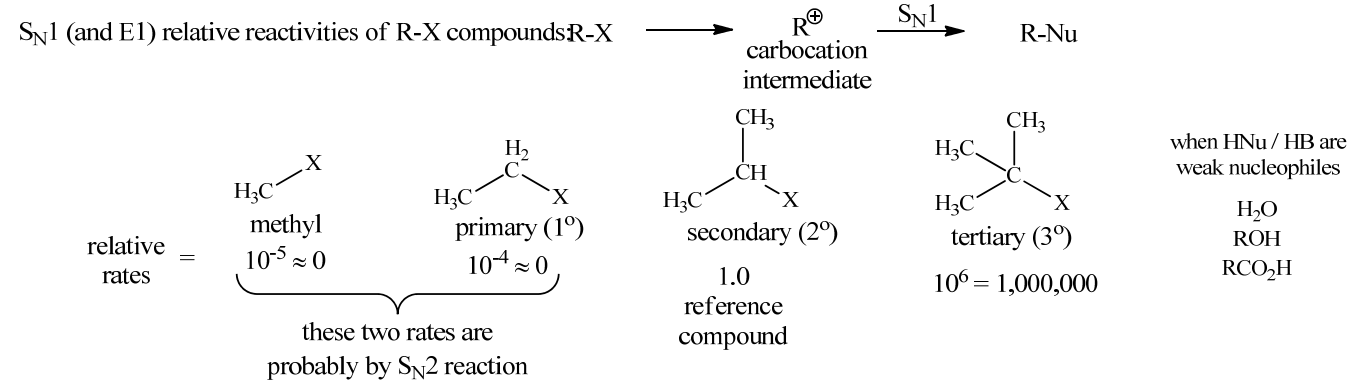
$$\text{Rate } S_N1 = k_{SN1}[RBr]^1 \qquad \text{Rate E1} = k_{E1}[RBr]^1$$

$$= \frac{(10)^{\frac{-Ea\,(SN)}{2.3RT}}}{(10)^{\frac{-Ea\,(E)}{2.3RT}}} = (10)^{\frac{-\Delta Ea}{2.3RT}}$$

Say $E_a(S_N) = 13$ kcal/mol and $E_a(E) = 14.6$ kcal/mol

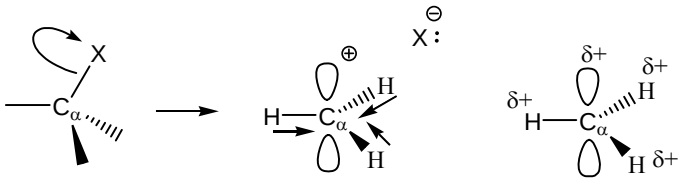
$$\frac{\text{Rate } S_N1}{\text{Rate E1}} = (10)^{\frac{-\Delta Ea}{2.3RT}} = (10)^{\frac{-(13-14.6)}{1.3}} = (10)^{\frac{1.6}{1.3}} = 10^{1.2} = \frac{40}{1}$$

R-X Substitution Pattern and rates of S_N1 reactions

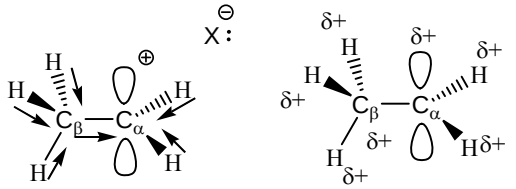


The order of stability at the electron deficient carbocation carbon is methyl << primary << secondary < tertiary. This is consistent with our understanding of inductive electron donating ability of alkyl groups compared to hydrogen. R groups (alkyl groups) are electron donating (an inductive effect). We observed, previously, that this helps alkene stability and makes it harder to form an anionic conjugate base in acid/base chemistry. A carbocation is extremely electron deficient (the opposite of a carbanion) and is very electronegative. Extra electron donation to a carbocation center proves very helpful. This can occur through an inductive effect or a resonance effect.

Inductive effects are proposed to occur via polarizations of sigma bonds in the organic skeleton, helping (or hurting) a center of reactivity. We can represent these in a carbocation center, simplistically, as shown below. Hyperconjugation is an alternative explanation to rationalize how extra electron density can be donated to the electron deficient carbocation carbon, but we will not use it in our course.

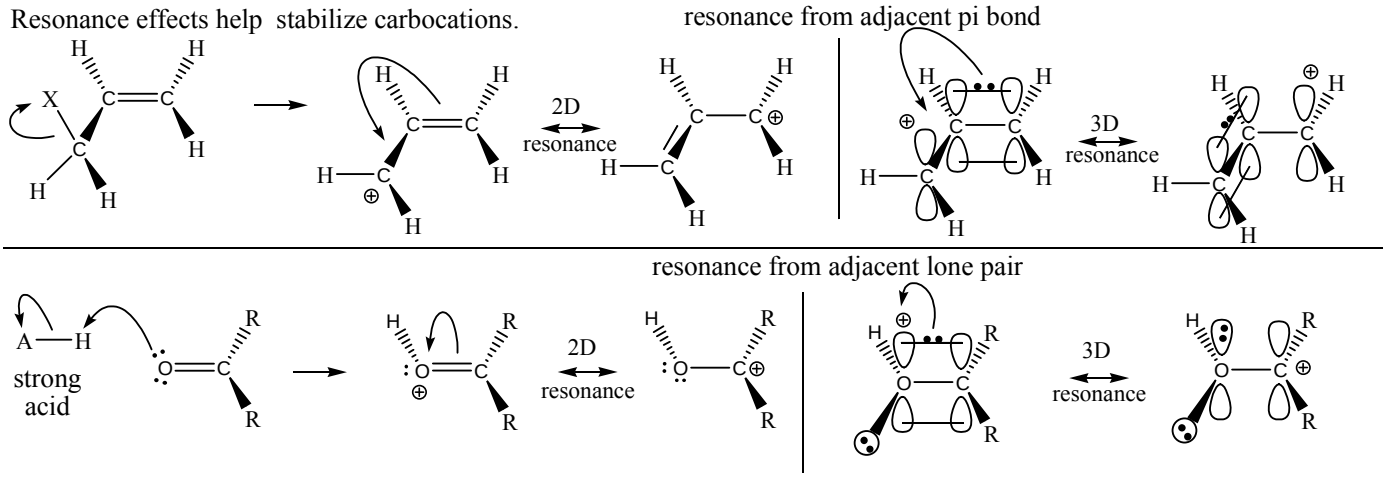


Sigma electrons are pulled toward the carbocation carbon. Part of the δ+ is distributed on to the hydrogen atoms, but not typically shown with formal charge.



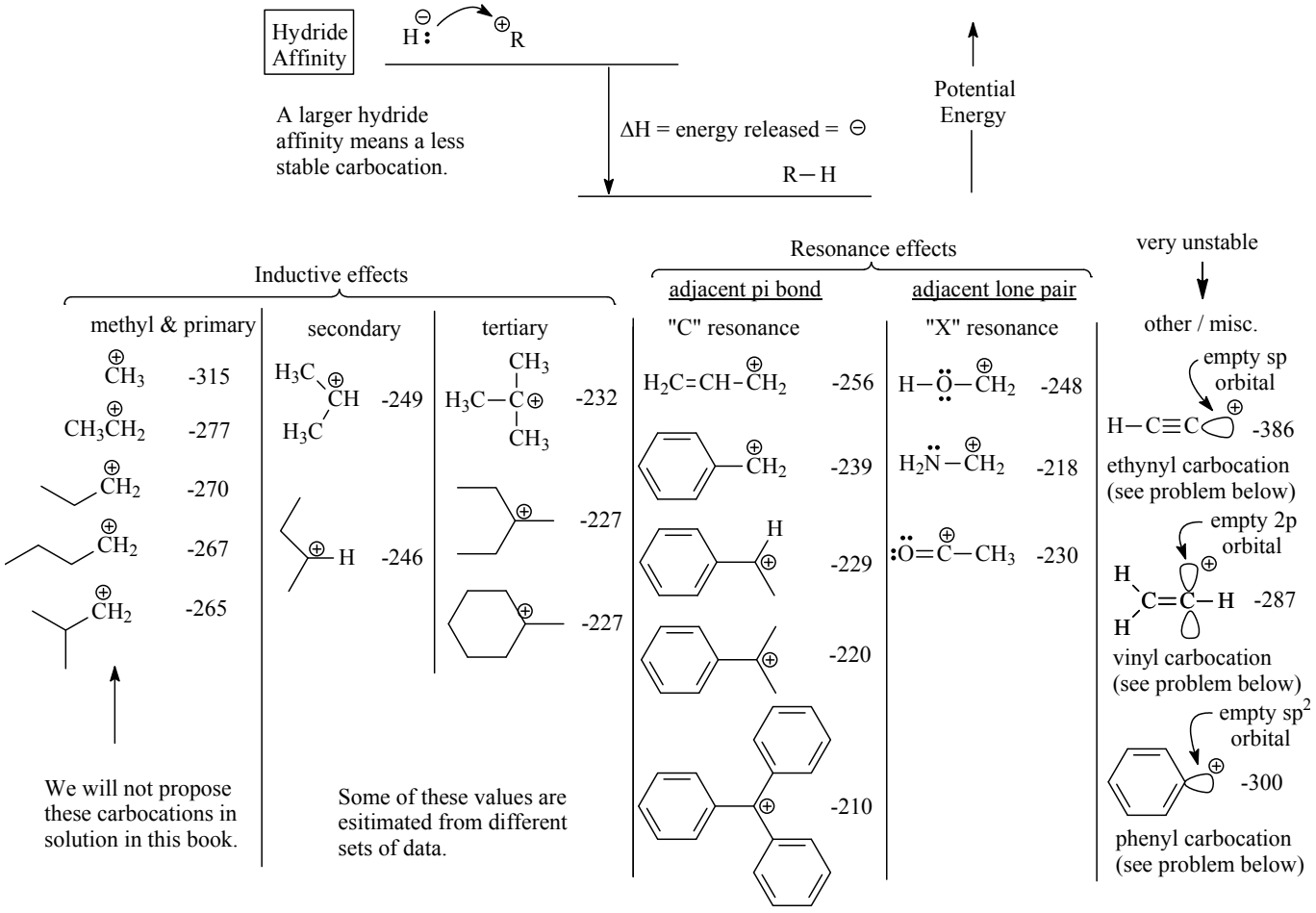
Additional sigma bonds of alkyl substituent(s) allow further polarizations of electrons from more bonds (inductive donating effect), which spreads out δ+ charge through sigma bond polarizations and helps stabilize the electron deficient carbocation carbon.

Resonance effects also make carbocations more stable. Allylic and benzylic RX compounds are very reactive in S_N1/E1 reactions (and S_N2 reactions). With resonance, there is actually full "pi electron" donation from an adjacent pi bond, instead of the inductive effect just mentioned above. An adjacent pi bond tends to produce greater stabilization of a carbocation than a single alkyl substituent. Resonance donation from lone pairs of heteroatoms can also be strongly stabilizing for carbocations. We will see such intermediates many times in later chapters.



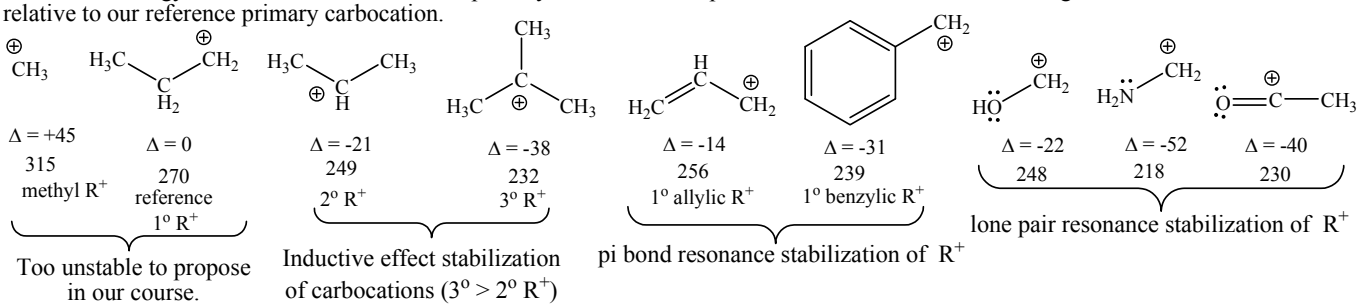
Gas phase Stabilities as Indicated by Hydride Affinities

Hydride affinity is the energy released when a hydride is added to a carbocation (gas phase reaction). The energy of reaction, ΔH, is very negative because the two reactive species (carbocation and hydride) are very unstable and the product formed is a stable molecule. How much do inductive and resonance effects help a carbocation center? The following gas phase data below show the differences in carbocation stability are enormous. In fact, differences are so large that we will almost never propose methyl or primary carbocation possibilities as reaction pathways in our course. We will consider these two patterns (CH_3-X and RCH_2-X) as unreactive in S_N1 and E1 chemistry, and that should make your life a little bit easier.



Problem 21 - Explain the differences in stability among the following carbocations (hydride affinities).

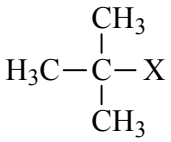
All relative energy values in kcal/mole versus a primary carbocation. A positive value is less stable and a negative value is more stable relative to our reference primary carbocation.



A more negative Δ is a more stable carbocation.

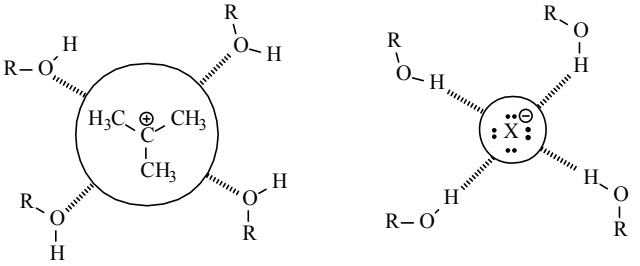
Problem 22 - Why are vinyl carbocations so difficult to form? (Hint – What is their hybridization?) How does an empty sp^2 orbital (phenyl carbocation) or empty sp orbital (ethynyl carbocation) compare to a typical sp^2 carbocation carbon with an empty 2p orbital? (An empty 2p orbital is also present on the vinyl carbocation, but the carbon hybridization is sp.)

Problem 23 – The bond energy depends on charge effects in the anions too. Can you explain the differences in bond energies below? (Hint: Where is the charge more delocalized?) We won't emphasize these differences.



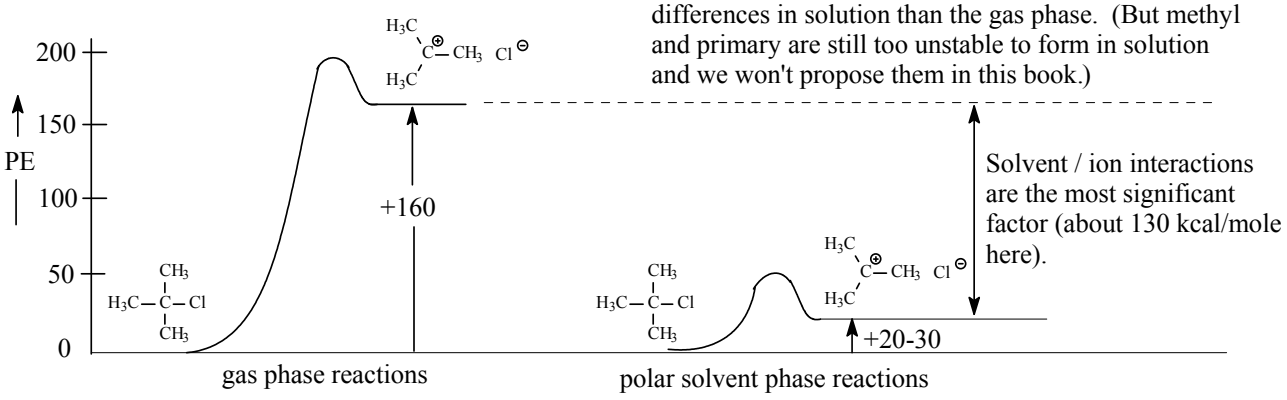
X =	Gas Phase B.E.
Cl	+157
Br	+149
I	+140

The activation energies for ionization in solvents are on the order of 20-30 kcal/mole (S_N1 and E1 reactions) It is clear from the difference in the gas phase energies of ionization that the solvent is the most stabilizing factor in ion formation. The magnitudes of these energies are compared in the potential energy diagram below. Because solvent structure is so complex we ignore it, but we do so at our own peril.



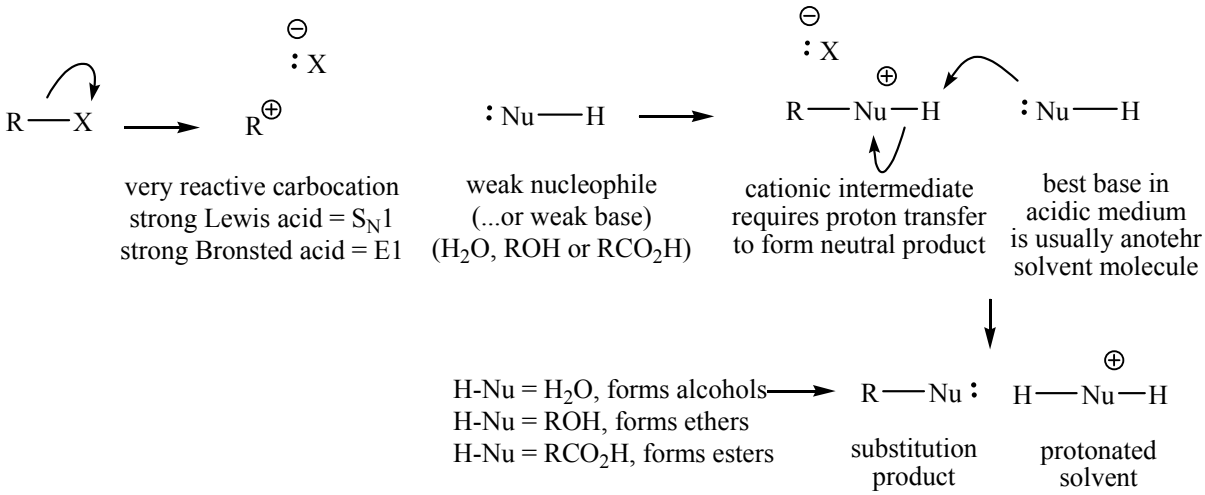
Many small solvent/ion interactions make up for a single, large covalent bond (heterolytic cleavage). A typical hydrogen bond is about 5-7 kcal/mole and typical covalent bonds are about 50-100 kcal/mole. In a sense the polar protic solvent helps to pull the C_α-X bond apart. The "polarized" protons tug on the "X" end and the lone pairs of the solvent molecules tug on the "C_α" end. If the carbocation is stable enough, the bond will be broken.

Carbocations are more stable and have smaller energy differences in solution than the gas phase. (But methyl and primary are still too unstable to form in solution and we won't propose them in this book.)



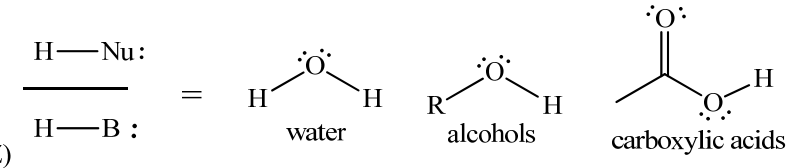
Weak Nucleophile/Bases are used in S_N1/E1 Reactions

We emphasize the term weak here because if the Nu: were strong (negative charge), the reactions observed would be S_N2/E2. Weak, for us, is represented by a neutral solvent molecule with a pair of electrons. For us, this will be a polar solvent molecule such as water (HOH), an alcohol (ROH) or a liquid carboxylic acid (RCO_2H). All of these are protic solvents, which are reasonably good at solvating both cations and anions. In every case, there is an extra hydrogen atom on the oxygen atom of a solvent molecule that must be removed in a final acid/base reaction to produce the neutral organic product. This protonated cationic intermediate results from the addition of water (H_2O, forms alcohols) or an alcohol (ROH, forms ethers) or a liquid carboxylic acid (RCO_2H, forms esters).

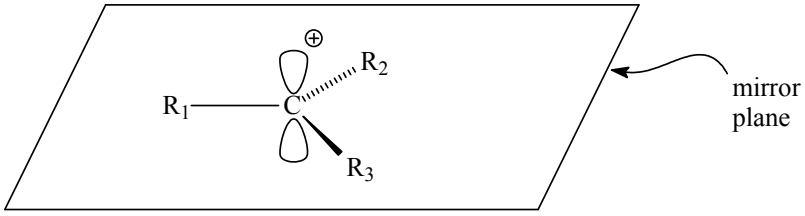


Weak electron pair donation in our course.

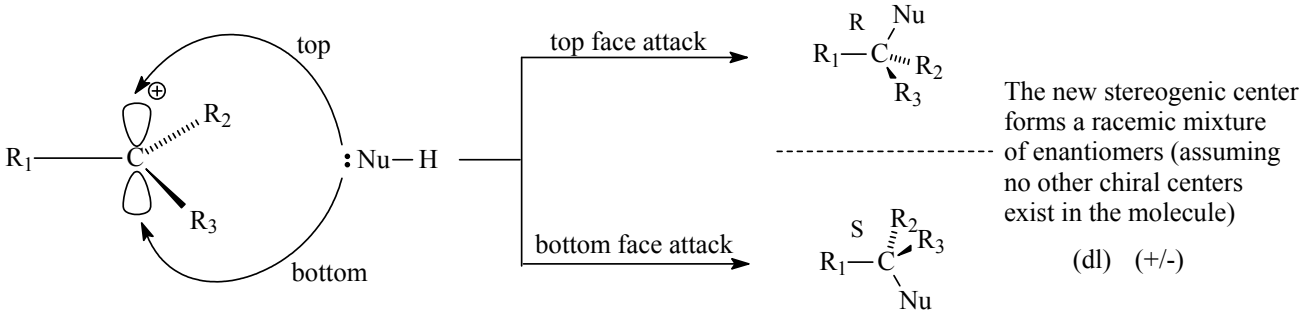
S_N1/E1 reactions
form carbocation (R^+) in first step,
R^+ has three common choices
1. rearrange to similar or more stable R^+
2. add nucleophile to top/bottom (R/S)
3. lose any beta proton from top/bottom (E/Z)
(forms pi bonds)



We will view the attack on an sp^2 carbocation as equally accessible from either face (top or bottom). Because carbocations are flat (in our simplistic view), attack is equally accessible from either face (top or bottom). The carbocation carbon, itself, is not chiral since it is sp^2 hybridized and only has three atoms attached to it. However, it is prochiral and can become chiral if the addition of a nucleophile brings in a fourth different group. This would lead to enantiomers, if this was the only chiral center. We are assuming that a 50/50 recemic mixture forms (in our course). It is also possible that there may be a stereogenic center somewhere else in the carbocation structure. Top and bottom attack would then lead to the formation of diastereomeric products.



achiral carbocation carbon



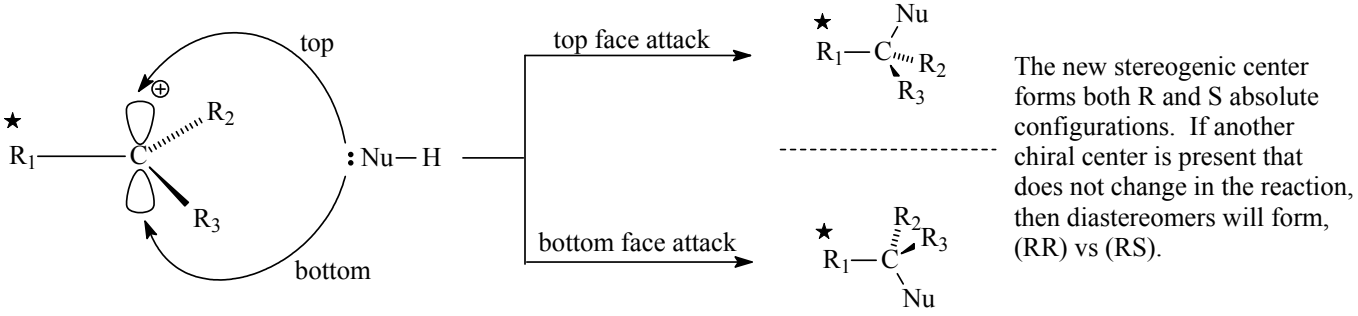
achiral carbocation carbon with no other chiral centers in R_1, R_2 or R_3

The new stereogenic center forms a racemic mixture of enantiomers (assuming no other chiral centers exist in the molecule)

(dl) (+/-)

R/S assumes priorities Nu > R1 > R2 > R3

If all three attached groups at a carbocation carbon are different from one another and the attacking nucleophile, then a racemic mixture of enantiomers will form.

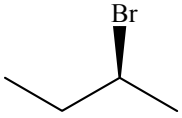


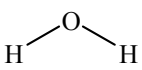
chiral branch in carbocation = ★

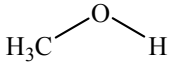
The new stereogenic center forms both R and S absolute configurations. If another chiral center is present that does not change in the reaction, then diastereomers will form, (RR) vs (RS).

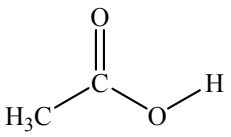
If one or more chiral centers were present in the carbocation, the top and bottom attack at the carbocation center would lead to diastereomers formed in unequal amounts.

Problem 24 – Draw in all of the mechanistic steps in an S_N1 reaction of 2R-bromobutane with a. water, b. methanol and c. ethanoic acid. Add in necessary details (3D stereochemistry, curved arrows, lone pairs, formal charge). What are the final products?



a. 

b. 

c. 

Donate the carbonyl (C=O) electrons to the carbocation.

S_N1 products will generally outcompete E1 products, in our course. The only exception for us (presented later) will be when alcohols are mixed with concentrated sulfuric acid at high temperatures to form alkenes (the E1 product).

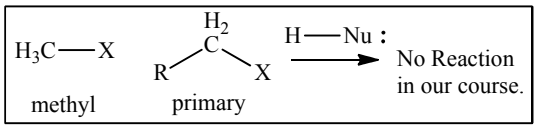
Keeping Track of the C_β Hydrogens in E1 Reactions (more possibilities than E2 reactions)

E1 products arise from the same carbocation intermediate formed in S_N1 reactions. Just as in E2 reactions, we have to examine each type of C_β-H. In more complicated R-X molecules there may be several different types of hydrogen atoms on C_β positions. After all, there can be either two or three C_β carbons with zero to three hydrogen atoms on each. We will only consider secondary and tertiary RX compounds below, since methyl and primary carbocations do not form (in our course). That still leaves a lot of possibilities.

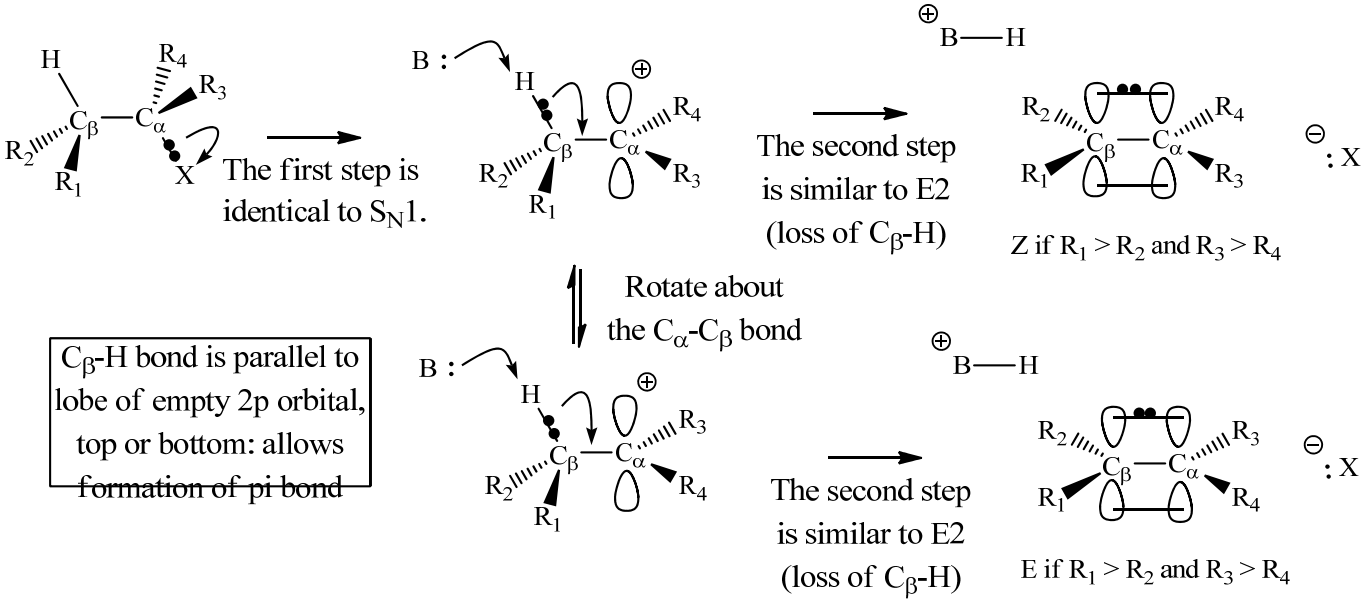
2^o R-X has six C_β positions

HNu: = H_2O, ROH, RCO_2H (weak, in our course)

3^o R-X has nine C_β positions



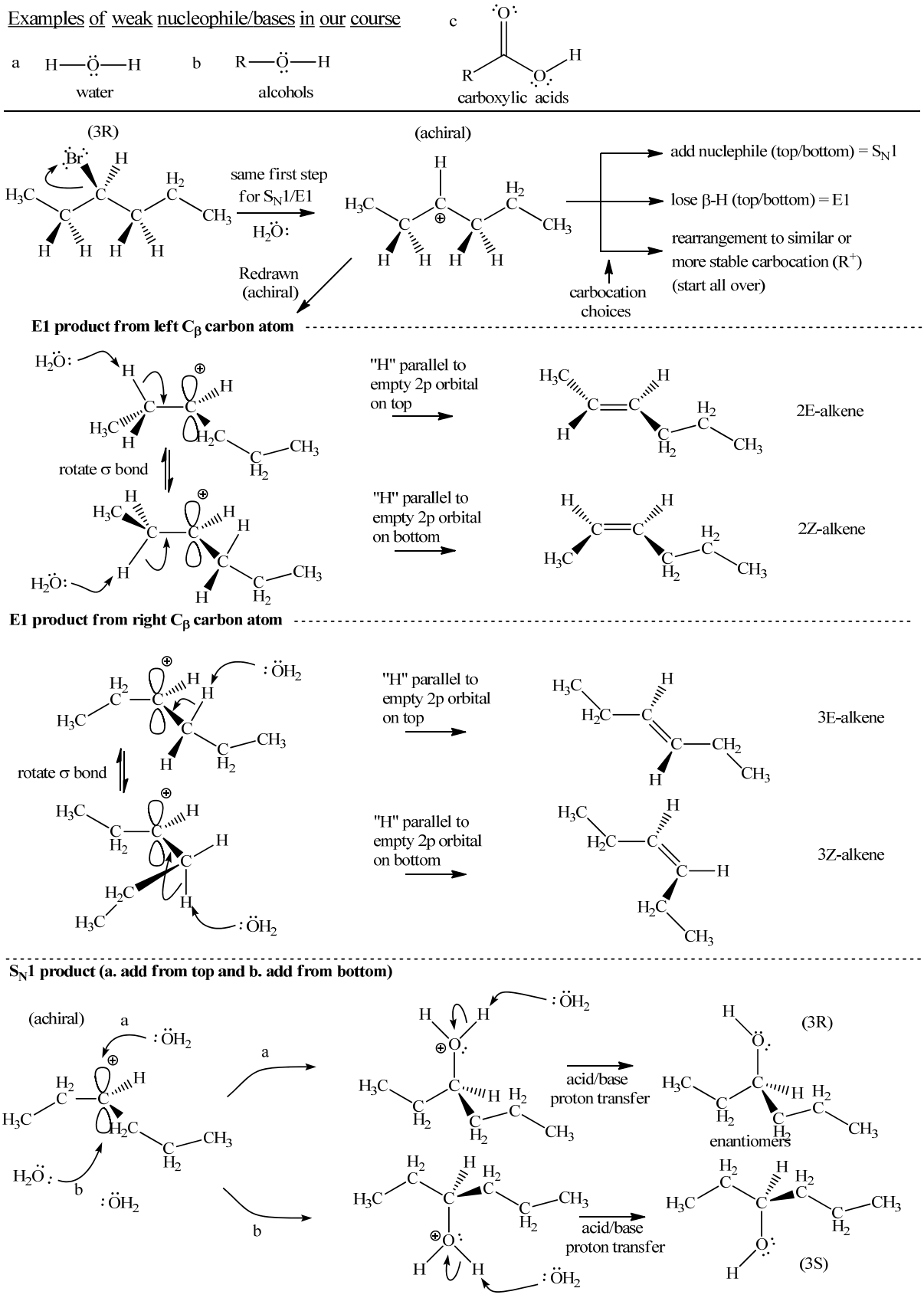
E1 Mechanism (unimolecular kinetics) loss of proton from any adjacent C_β-H position, top or bottom



The high reactivity (low stability) of carbocations forces some very quick choices to try and stabilize the situation. The carbocation needs two electrons to complete its octet (in a hurry!). There are three ways it typically does this. We have studied the two ultimate pathways, S_N1 and E1 reactions.

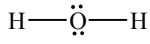
The third possibility, rearrangements, is discussed next. Rearrangements are a temporary solution for an unstable carbocation. Rearrangements transfer the unstable carbocation site to a new position having a similar energy or, better yet, to a site where the positive charge is more stable. If such possibilities exist, this will very likely be one of the observed reaction pathways. However, even with a rearrangement a carbocation will not gain the two needed electrons. The electron deficiency is merely moved to a new position. This process can occur a number of times before a carbocation encounters its ultimate fates, discussed above, S_N1 and E1.

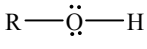
S_N1 / E1 possibilities –extra complications at C_β positions, In this problem 2° RX, rearrangements are NOT considered (H_2O,ROH,RCO_2H)

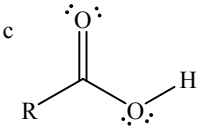


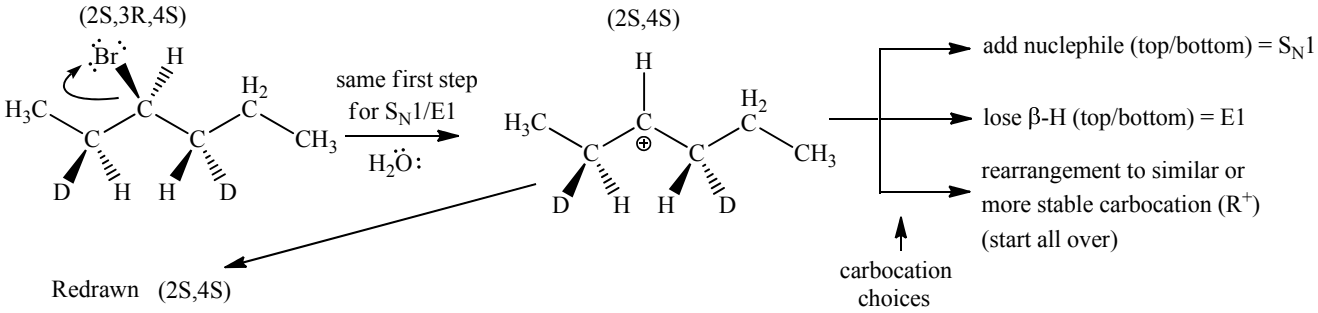
S_N1 / E1 possibilities –extra complications at C_β positions, 2° RX, rearrangements NOT considered, with deuterium (makes it a little harder)

Examples of weak nucleophile/bases

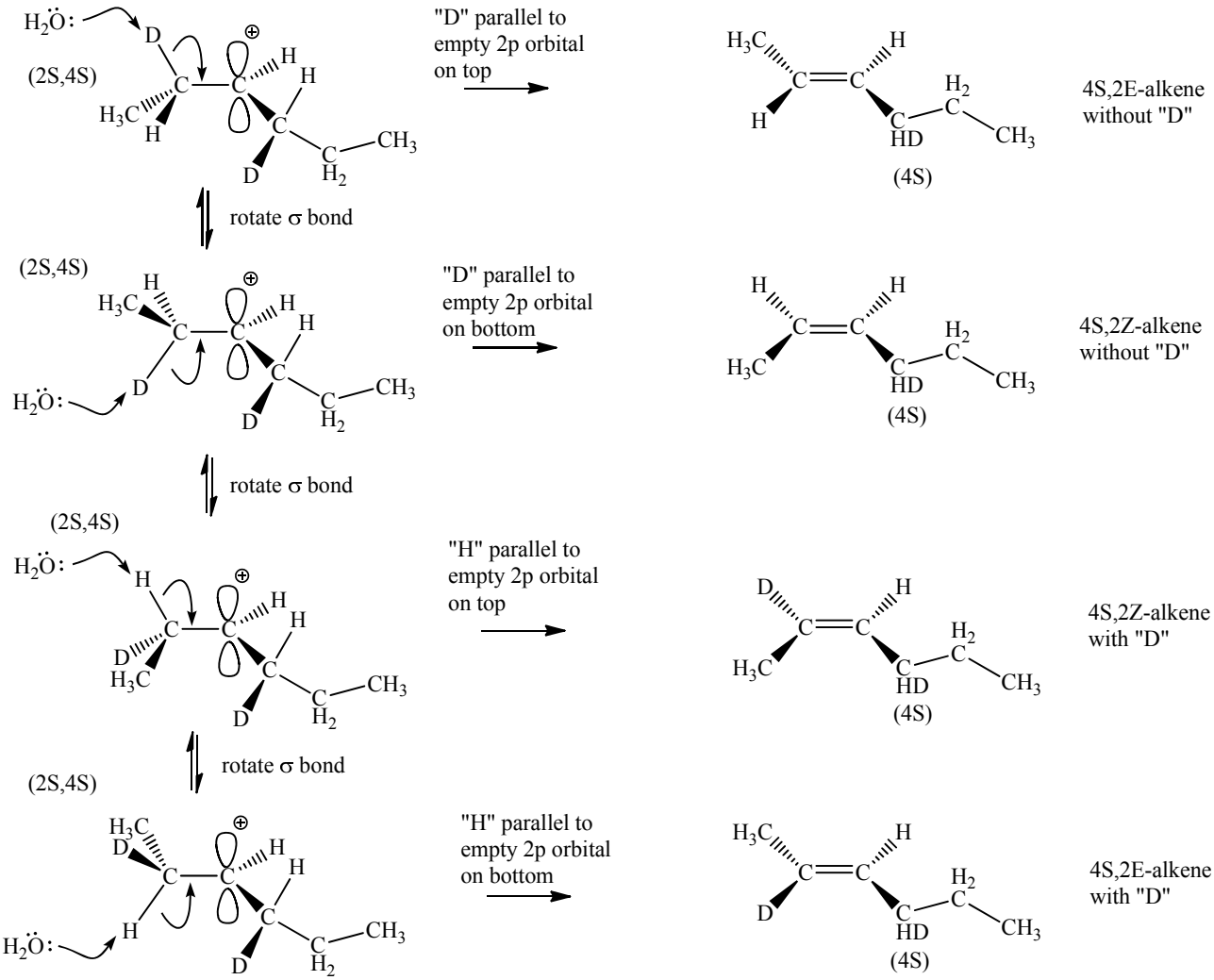
a  water

b  alcohols

c  carboxylic acids

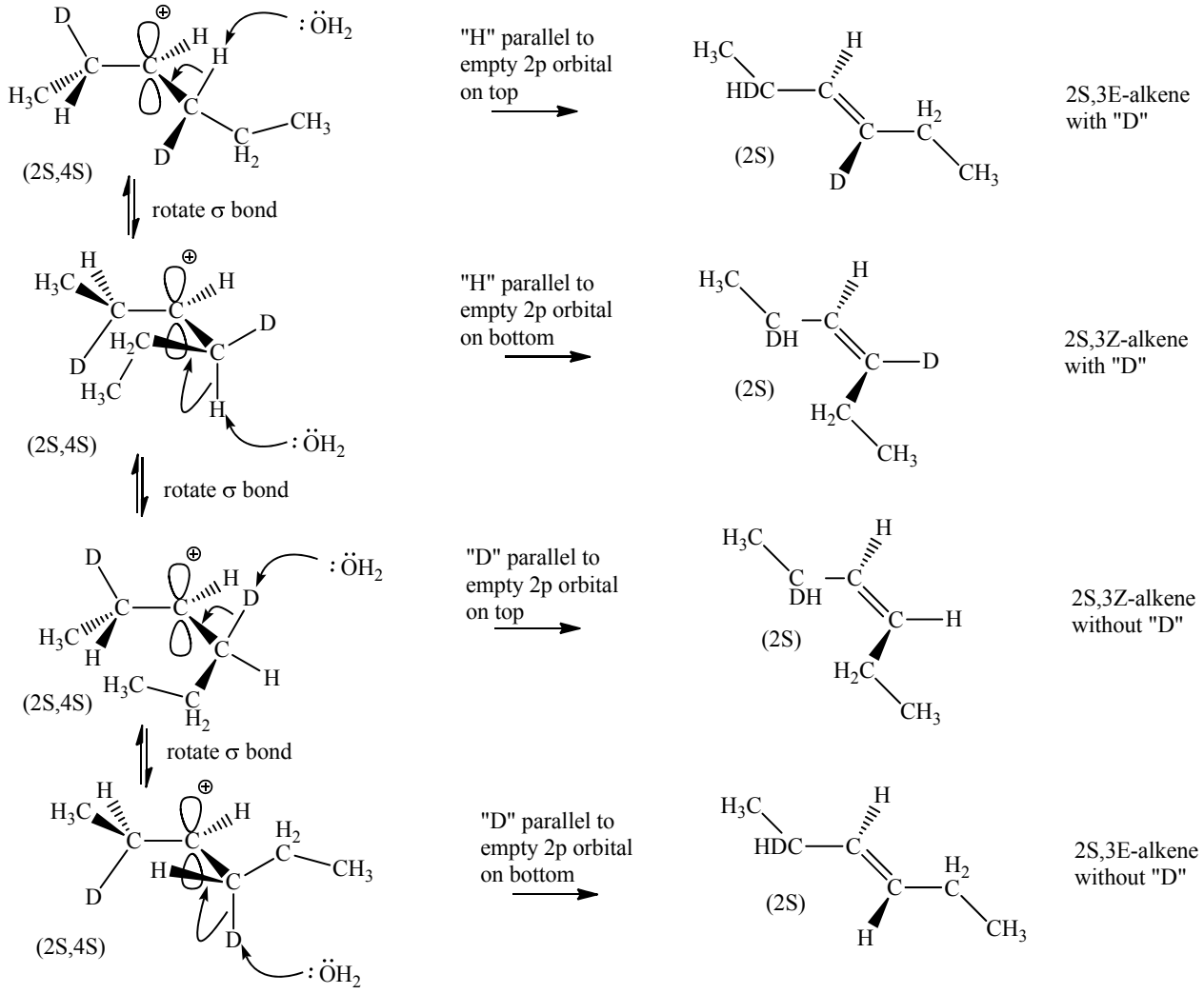


E1 products from left C_β carbon atom (4 possible alkenes from the left C_β carbon)

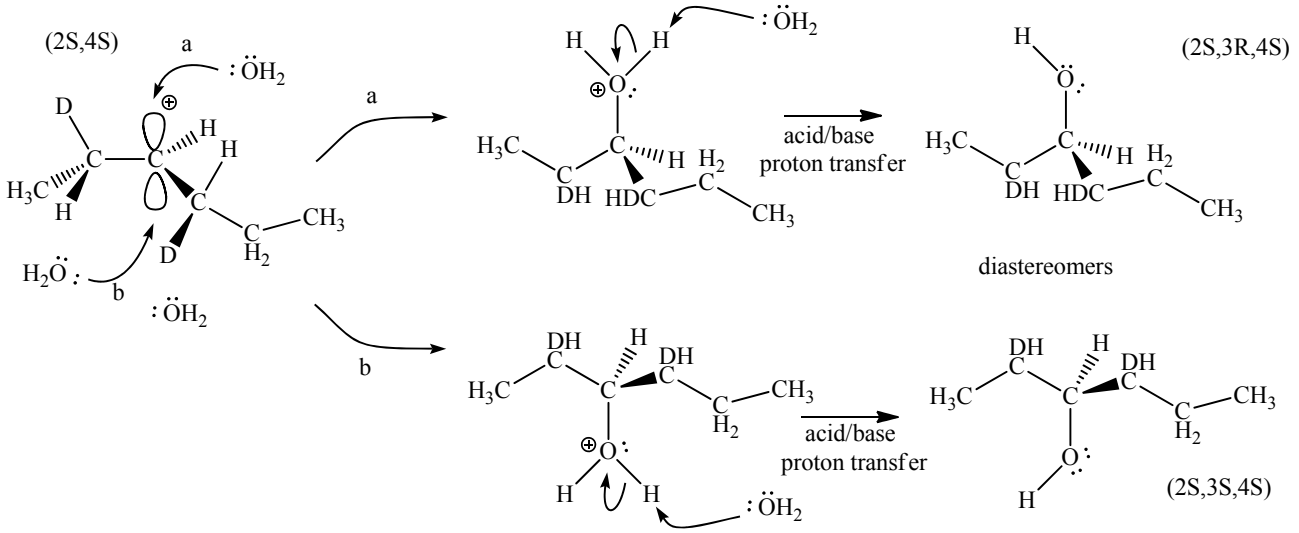


Redrawn from above (2S,4S)

E1 products from right C_β carbon atom (4 possible alkenes from the left C_β carbon)

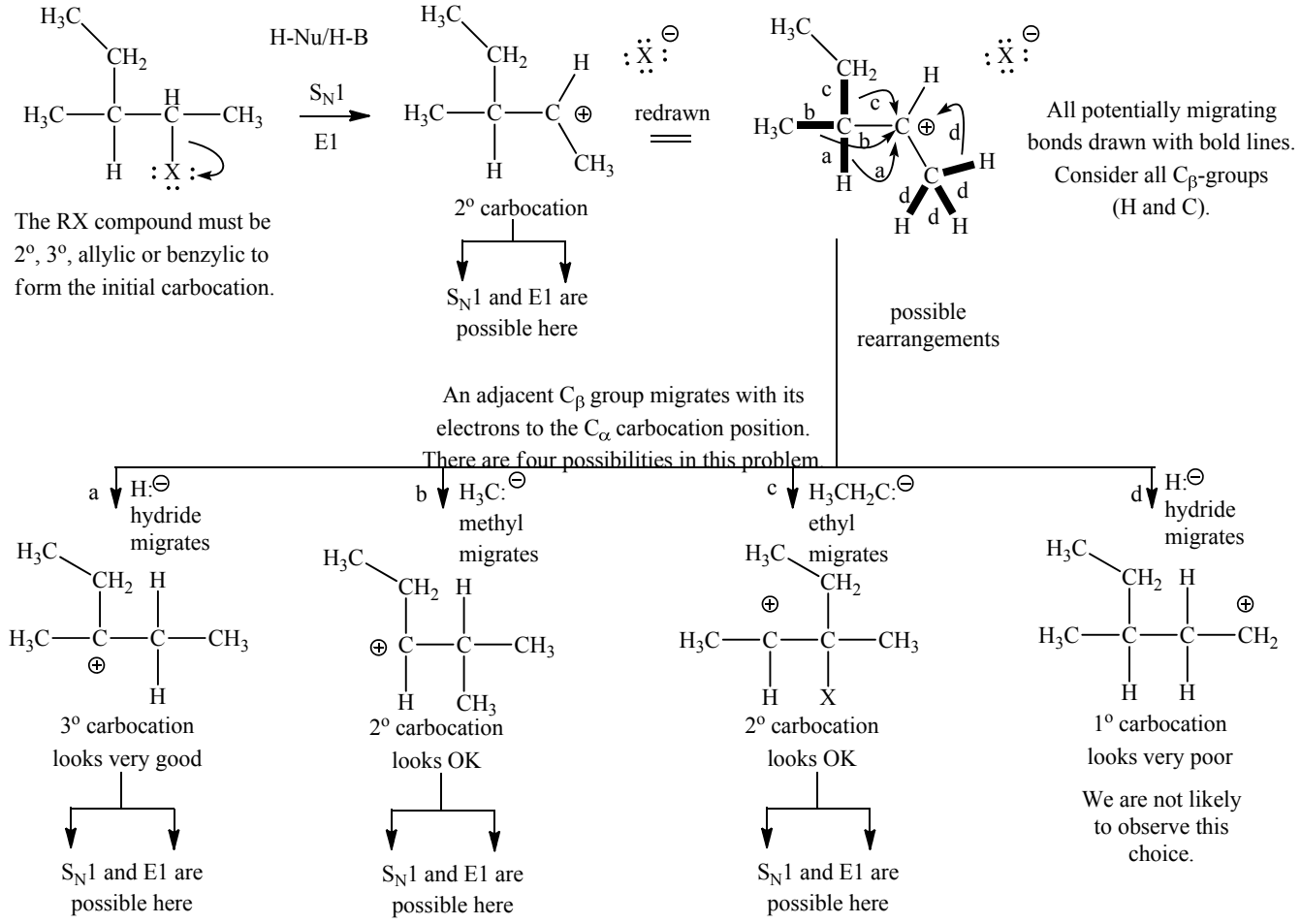


S_N1 products (a. add from top and b. add from bottom)



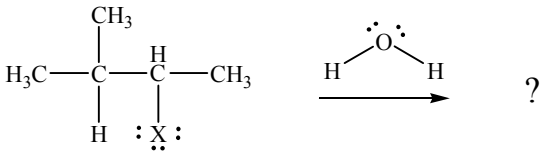
Rearrangements of Carbocations

As we have seen, carbocations have very large potential energy differences. These differences provide a large driving force to form more stable carbocations from less stable carbocations, in the range of ≈15-20 kcal/mole in the gas phase for 1° to 2° and 2° to 3° choices. Rearrangements are a competitive pathway in any reaction where a carbocation is formed. A relatively simple example illustrates the necessity to be systematic in your approach to determine all of the varied possibilities. Consider the migration of every group on a C_β position, whether H or C. To keep our choices simpler (than they really are) we will only consider rearrangements of 2° to 3° and 3° to 3° carbocations.



Problem 25 – What are the likely S_N1 and E1 products of the initial carbocation and the rearranged carbocations from "a", "b" and "c"?

Problem 26 – Write out your own mechanism for all reasonable products from the given R-X compound in water (2-halo-3-methylbutane).

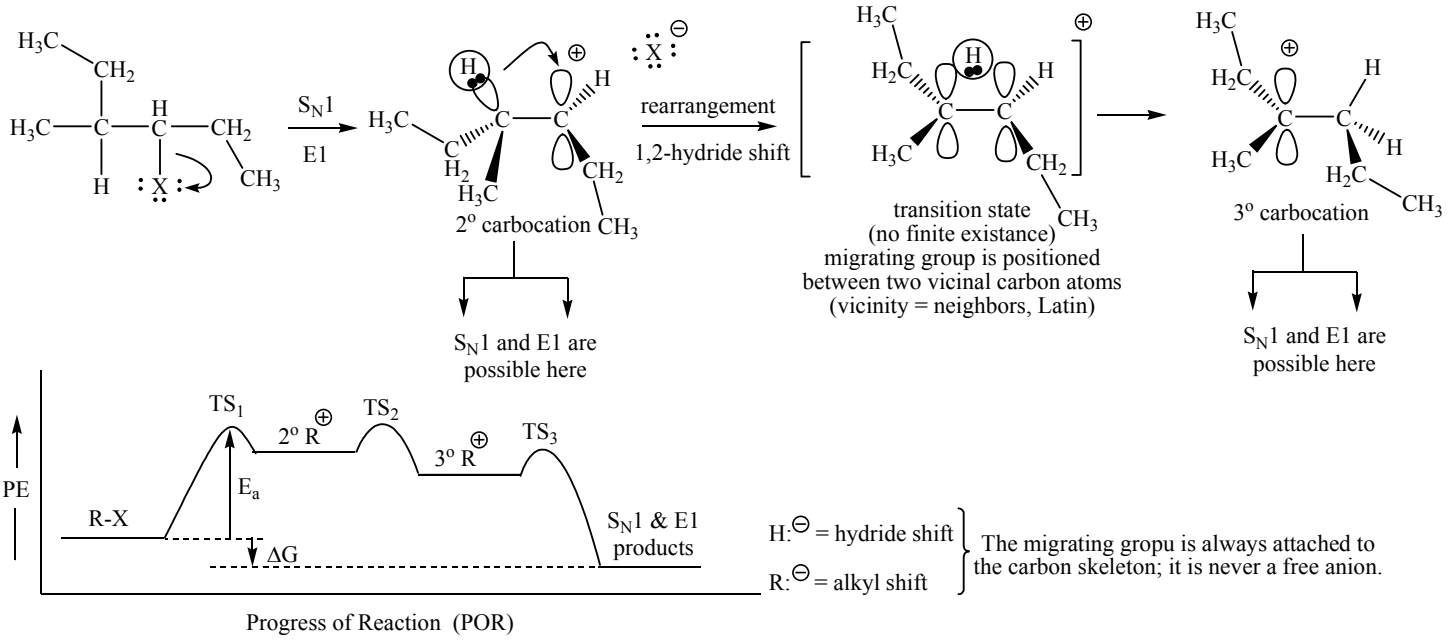


The most competitive rearrangement above will be to form the more stable tertiary carbocation from the initially formed secondary carbocation. It is also likely that at least some of the initially formed carbocation will react by the S_N1 and E1 choices. However, those may be minor products when a much more stable carbocation can

form by rearrangement. In the end, S_N1 and E1 possibilities are the ultimate fates of even the most stable carbocation that can form. Our goal at this point is to understand how rearrangements occur and what S_N1 and E1 products are possible.

All groups on any C_β carbon can potentially migrate to the adjacent carbocation carbon (also called a 1,2 shifts), if a similar or more stable carbocation can form. If hydrogen with its two electrons is the group migrating, the rearrangement is called a 1,2 hydride shift. If a carbon group migrates with its two electrons, the rearrangement if called a 1,2 alkyl shift. Hydride and alkyl shifts can occur from further away than a C_β position or even between two positions in completely different molecules. However, these we will not emphasize such possibilities in our course.

Transition state of a carbocation rearrangement

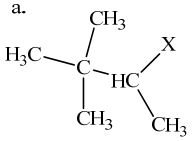


Two main rules will help guide you in evaluating possible rearrangements.

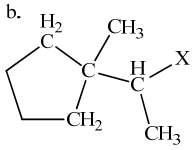
1. Rearrangements usually occur so that the migrating groups moves from a C_β atom to the C_α atom (the carbocation center). These are the 1,2 hydride or 1,2 alkyl shifts mentioned above. The C_β atom that gives up the migrating group becomes the new electron deficient carbocation center, often because it is a more stable carbocation site.

2. If a 1,2 shift of a hydrogen atom or an alkyl group can form a similar or more stable carbocation, then such a rearrangement is likely to be competitive with other reaction choices (S_N1 and E1). When *interpreting* a reaction mechanism involving rearrangements, you may have to consider both equal ($3^o \rightarrow 3^o R^+$) and more stable ($2^o \rightarrow 3^o R^+$) carbocation possibilities. However in this book when you are asked to *predict* what might be possible, you usually only need to consider more stable carbocation possibilities ($2^o \rightarrow 3^o R^+$).

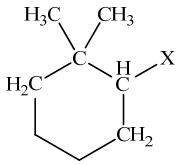
Problem 27 - Consider all possible rearrangements from ionization of the following RX reactants. Which are reasonable? What are the possible S_N1 and E1 products from the reasonable carbocation possibilities?

a. 

initial R+	subsequent R+
$S_N1 = 2$	$S_N1 = 1$
E1 = 1	E1 = 2

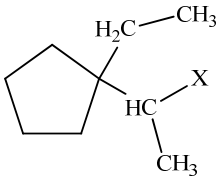
b. 

initial R+	subsequent R+
$S_N1 = 2$	$S_N1 = 4$
E1 = 1	E1 = 6

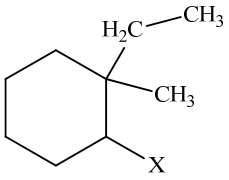
c. 

initial R+	subsequent R+
$S_N1 = 2$	$S_N1 = 4$
E1 = 1	E1 = 6

d. What would happen to the complexity of the above problems with a small change of an ethyl for a methyl? Use the key of "b" and "c" as a guide. This problem is a lot more messy than those above, (which is the point of asking it). There are too many possibilities to consider listing every answer.

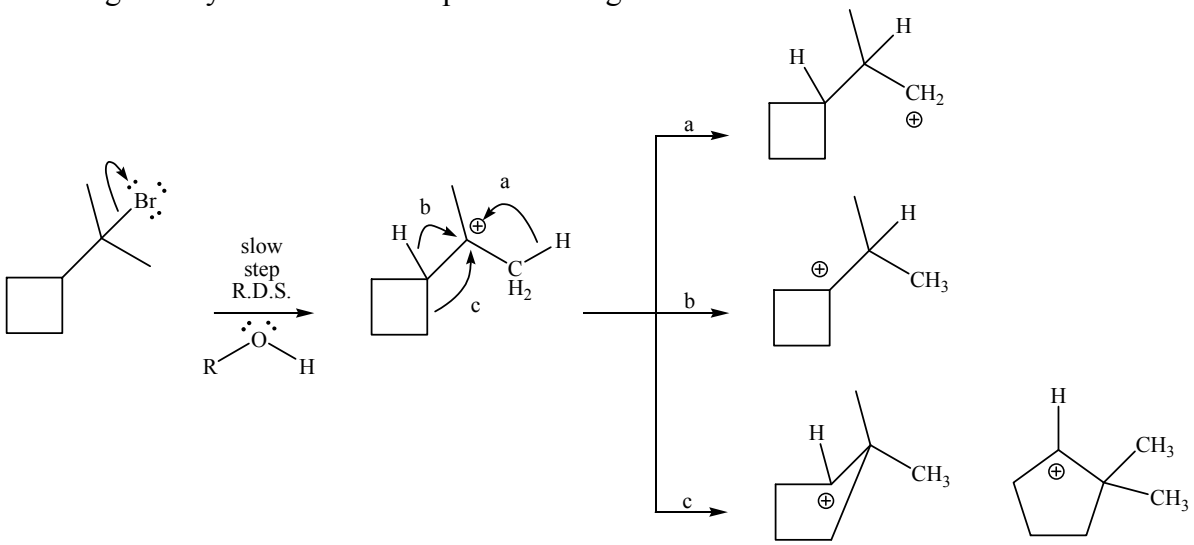


initial R+	subsequent R+
$S_N1 = 2$	$S_N1 = 7$ (?)
E1 = 1	E1 = 12 (?)



similar

There are other features that must also be considered in carbocation rearrangements in addition to the relative stabilities of 1^o, 2^o and 3^o carbocations. One such feature that modifies the relative potential energies of the possible choices is strain energy. Consider the possible rearrangement choices available to the following tertiary carbocation in a polar ionizing solvent.

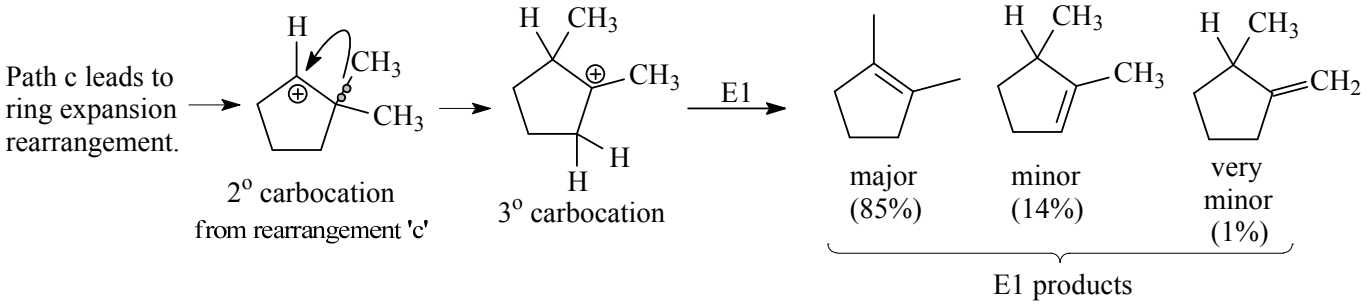


a. A hydride migration makes a primary carbocation from a tertiary carbocation. This reaction would increase the potential energy by about 35 kcal/mole and is not a realistic option.

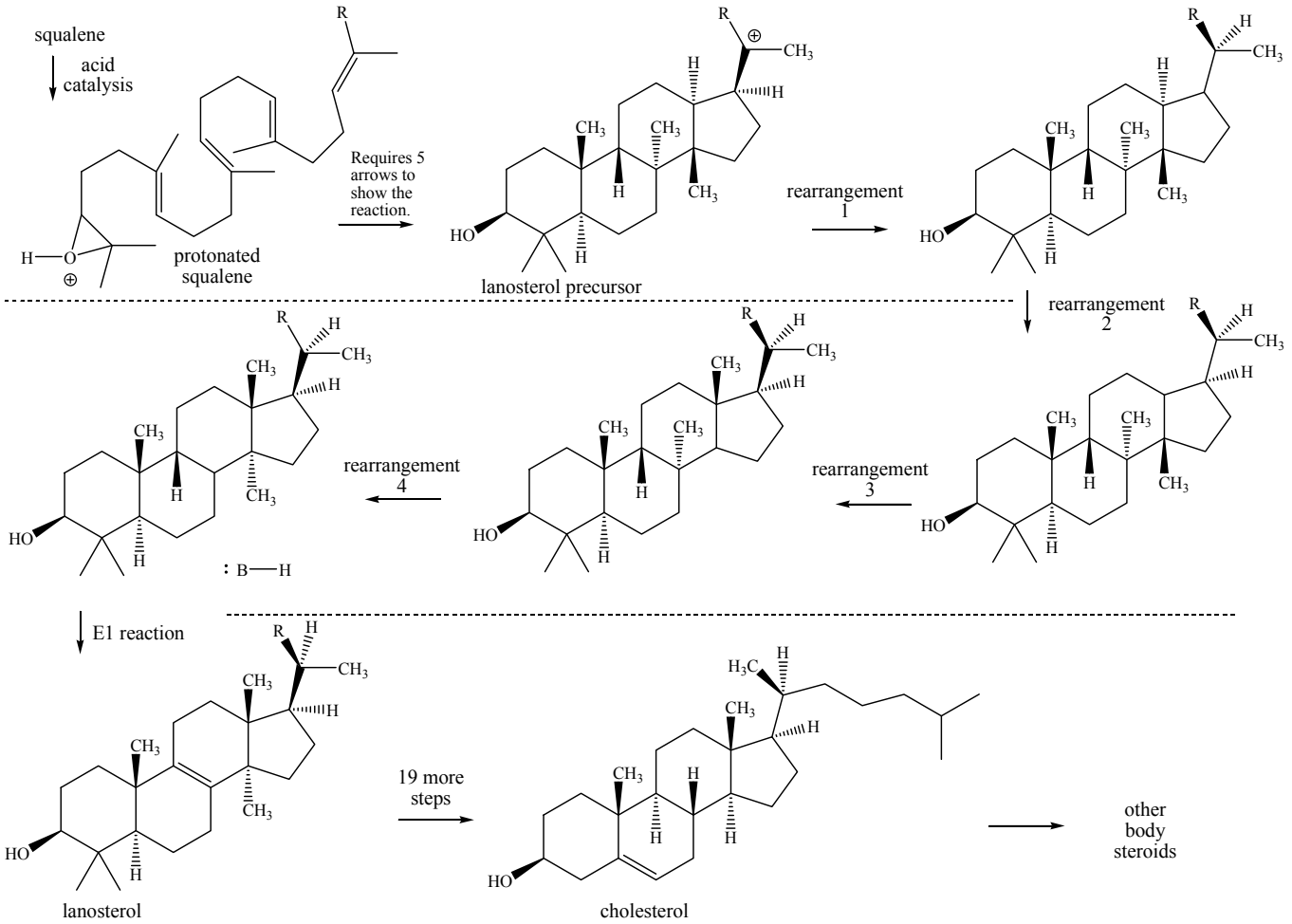
b. At first this option (hydride shift) seems very reasonable (tertiary carbocation to tertiary carbocation), but there would be much additional ring strain energy because of bond angle changes in the small cyclobutane ring (109o = sp3 to 120o = sp2), while geometric shape in the ring is trying to be 90o. This would, therefore, not be a favorable option.

c. At first this looks like a very poor reaction (tertiary carbocation to secondary carbocation vial alkyl migration of a ring carbon) and would be uphill by about 15 kcal/mole based on carbocation stabilities. However, the reduction in ring strain would be downhill by about 20 kcal/mole (26 kcal/mole → 6 kcal/mole), resulting in an overall potential energy change of -5 kcal/mole.

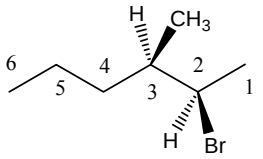
What is actually observed? (Only E1 reactions are shown, S_N1 possibilities are not included.)
Rearrangement 'c' occurs, followed by another rearrangement from a secondary to tertiary carbocation.



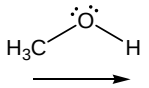
Problem 28 – Lanosterol is the first steroid skeletal structure on the way to cholesterol and other steroids in our bodies. It is formed in a spectacular cyclization of protonated squalene oxide. The initially formed 3° carbocation rearranges 4 times before it undergoes an E1 reaction to form lanosterol. Add in the arrows and formal charge to show the rearrangements and the final E1 reaction.



Example S_N1 / E1 Mechanisms with rearrangement



2R-bromo-3R-methylhexane

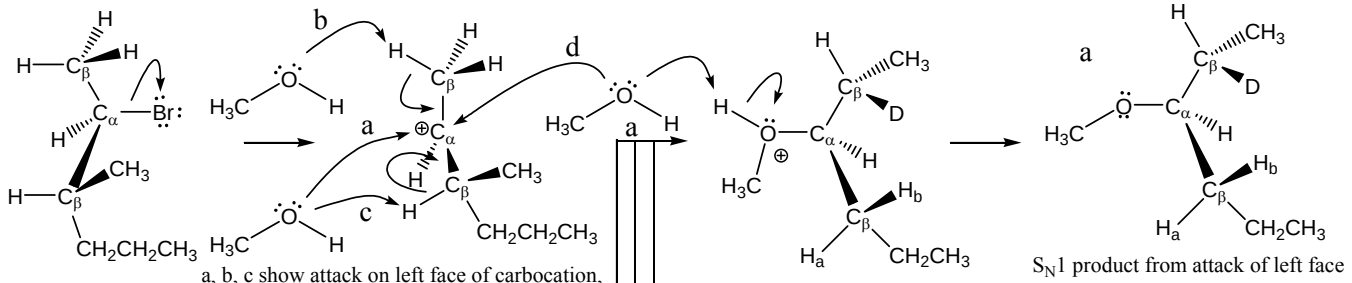


secondary RX (2°)

1. weak H-Nu:/H-B:
2. 2° R-X

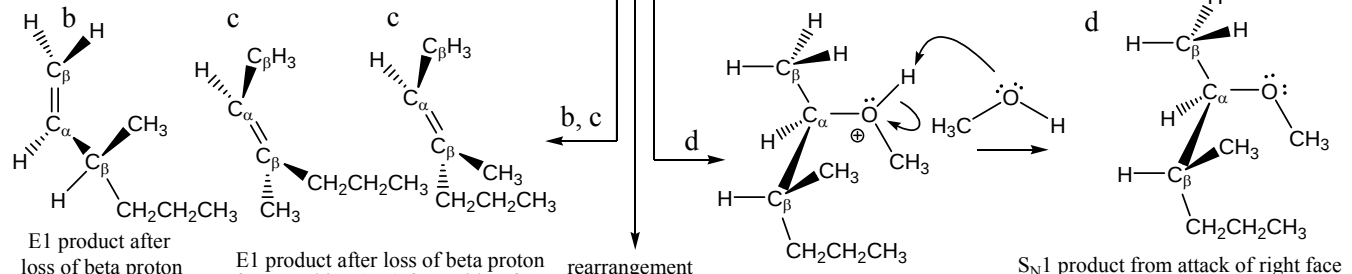
1. The first 2° R^+ forms two S_N1 products and three E1 products
2. The rearranged 3° R^+ forms two S_N1 products and five E1 products

R^+ reactions → 1. add H-Nu: (S_N1)
2. lose C_β-H (E1)
3. rearrange (start over)



a, b, c show attack on left face of carbocation, attack also occurs from the right side of R^+.

S_N1 product from attack of left face



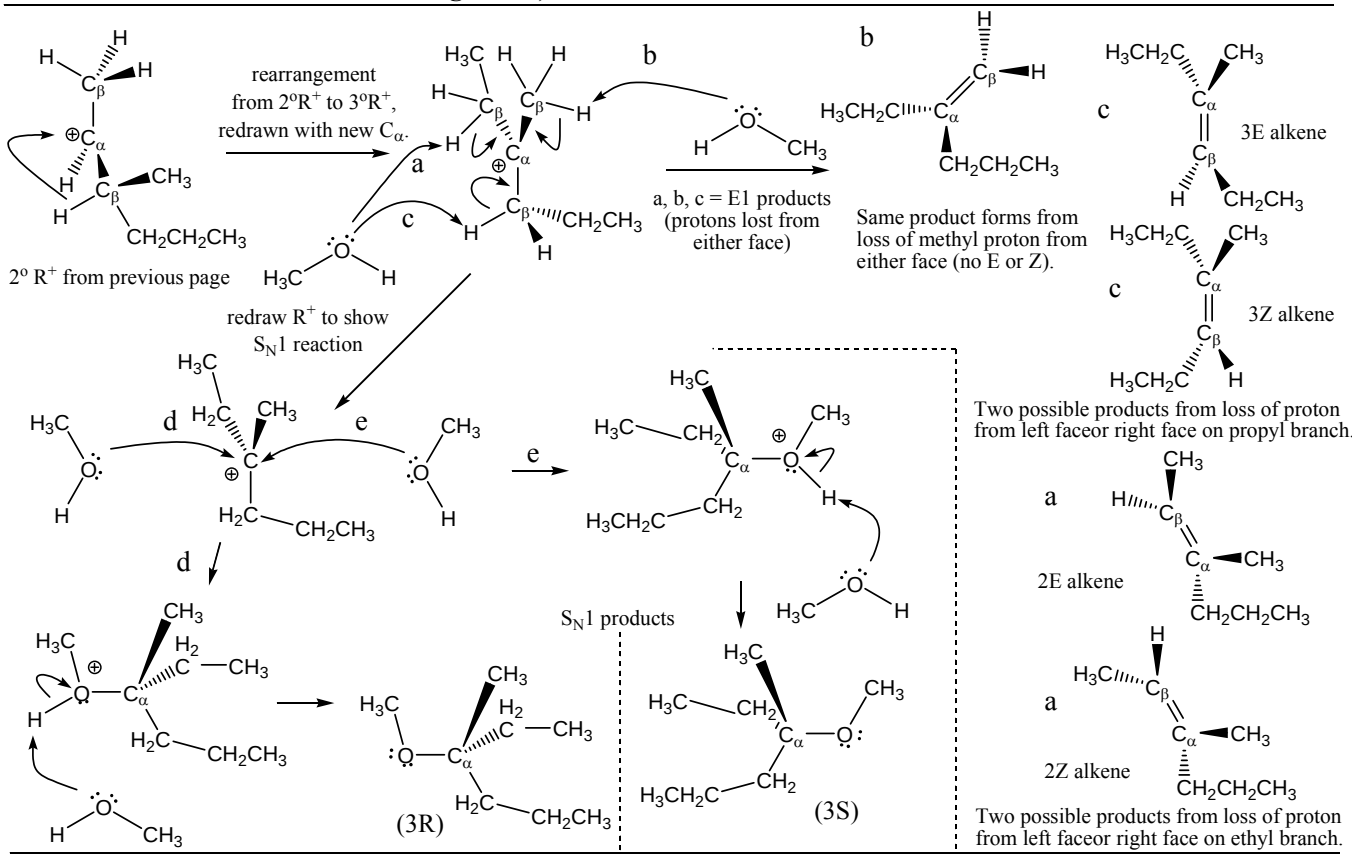
E1 product after loss of beta proton from methyl (CH_3)

E1 product after loss of beta proton from methine (CH) from either face

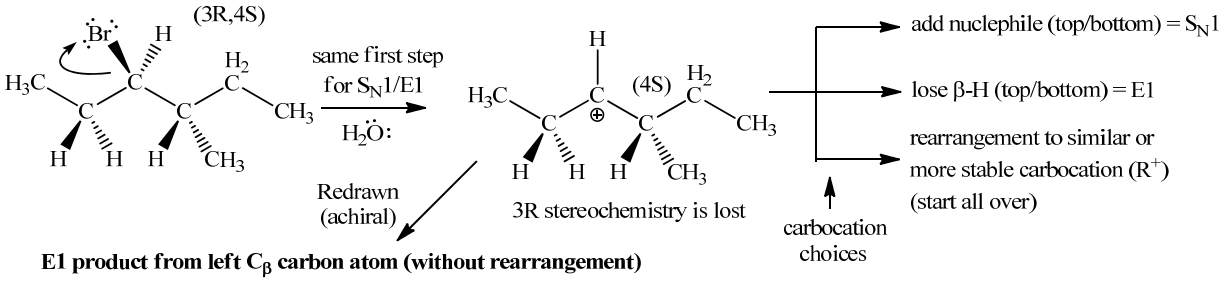
rearrangement (next page)

S_N1 product from attack of right face

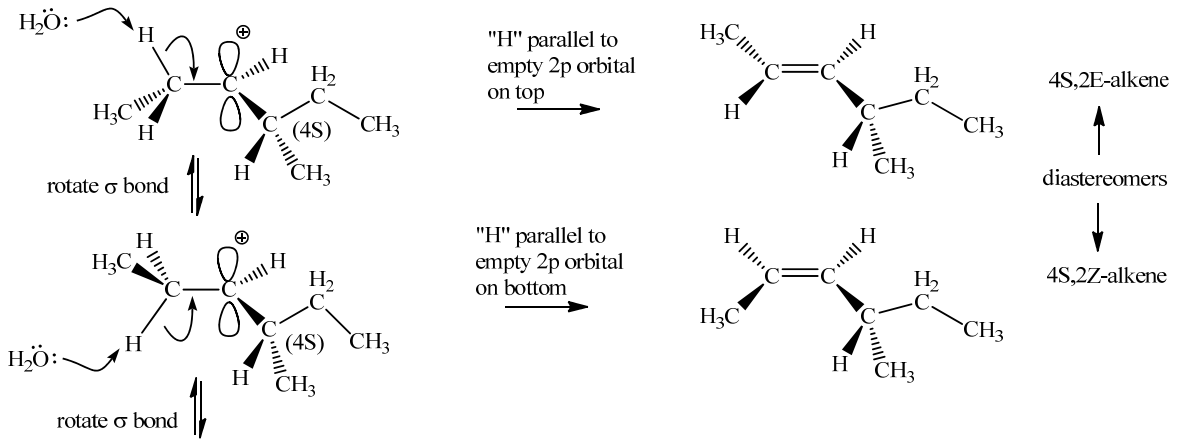
carbocation continued with rearrangement)



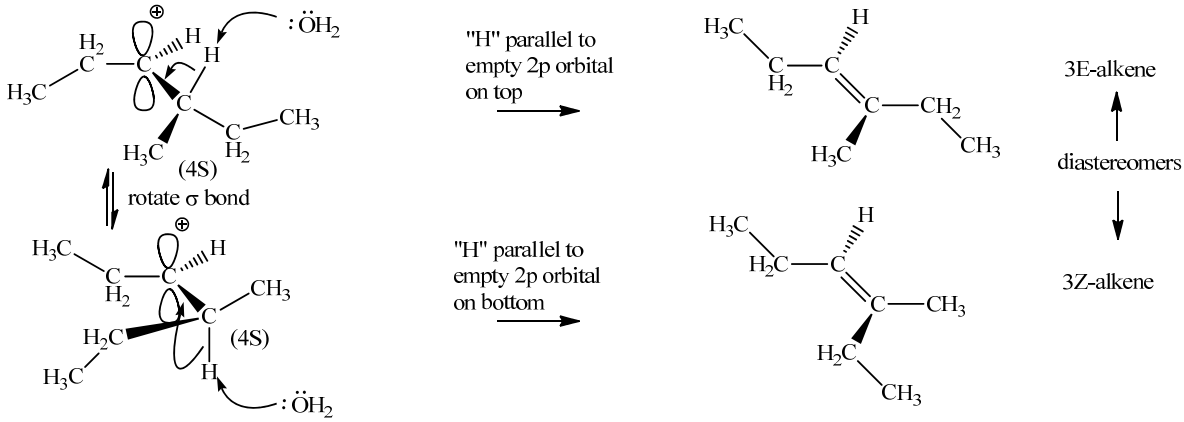
S_N1 / E1 possibilities –extra complications at C_β positions of 2° RX, rearrangement to more stable 3° R^+ considered



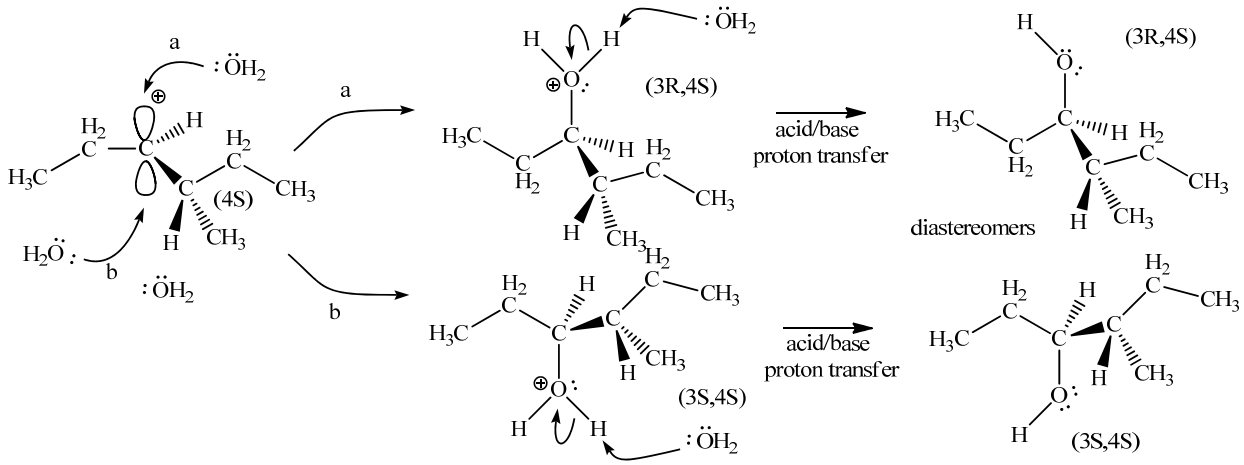
E1 product from left C_β carbon atom (without rearrangement)



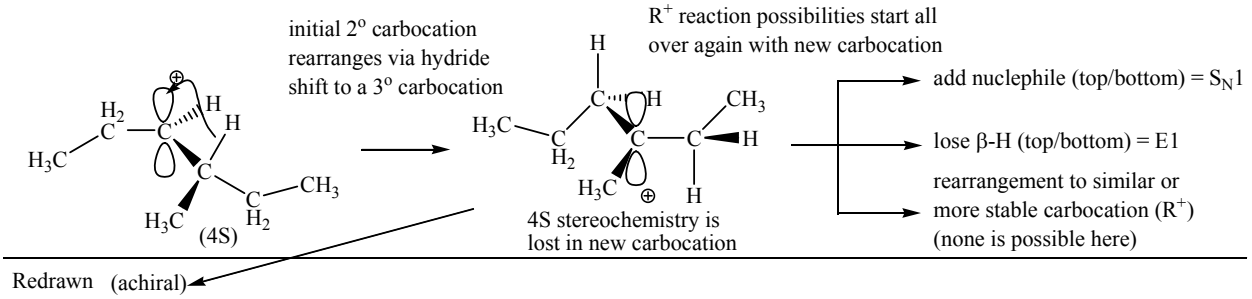
E1 product from right C_β carbon atom (without rearrangement)



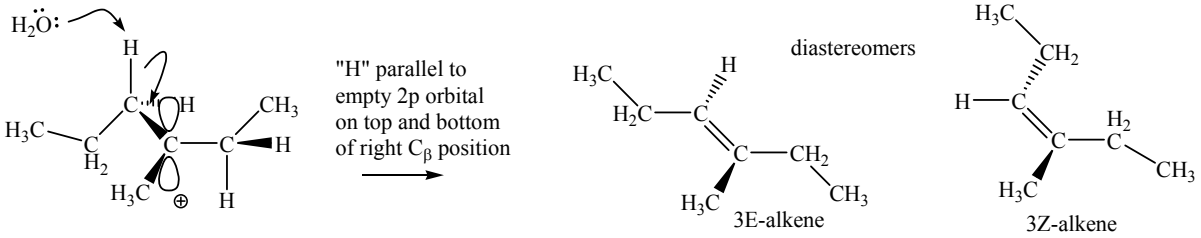
S_N1 product (a. add from top and b. add from bottom), (without rearrangement)



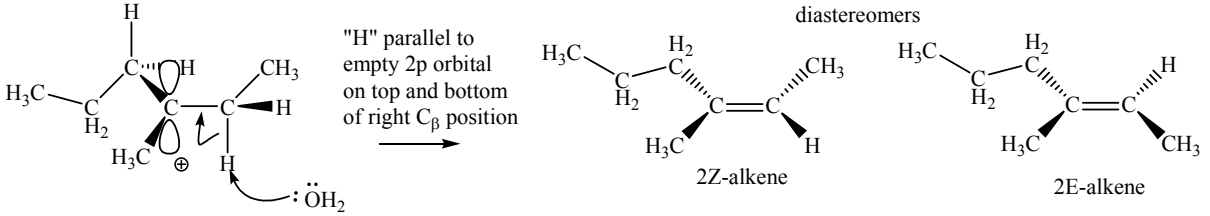
After rearrangement to 3° carbocation (R^+) – We will skip rearrangements in Chem 314



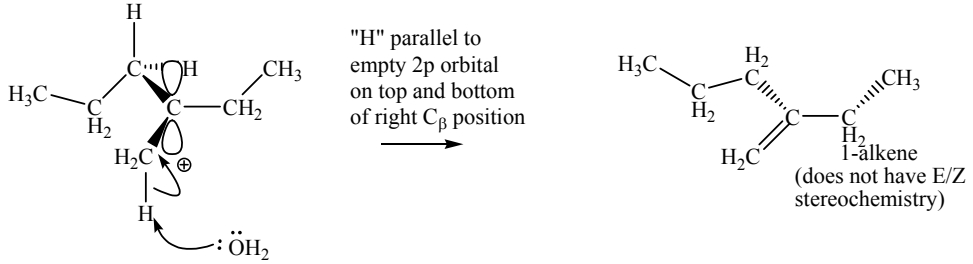
E1 products from left C_β carbon atom (top and bottom, after rearrangement)



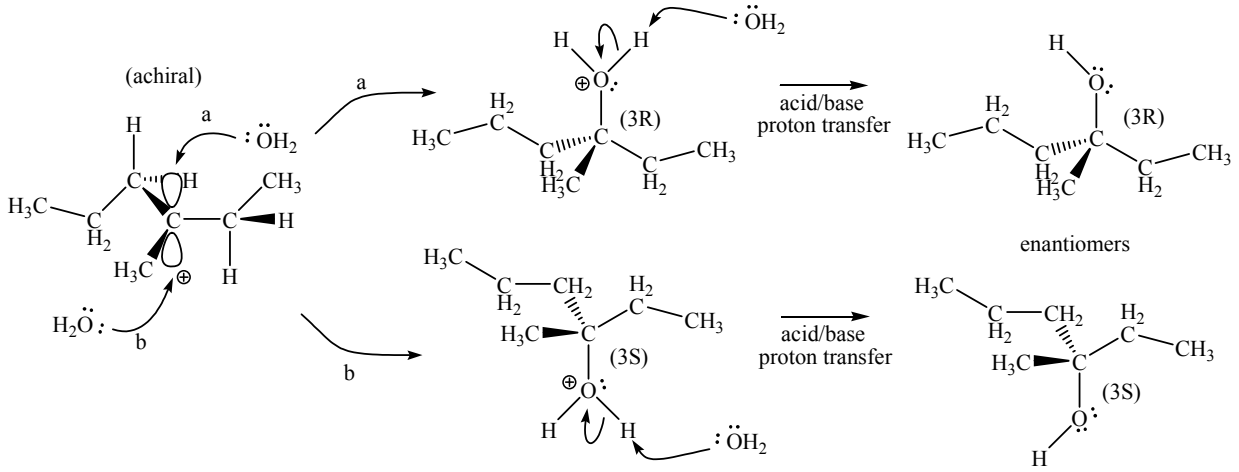
E1 product from right C_β carbon atom (top and bottom, after rearrangement)



E1 product from methyl C_β carbon atom (top and bottom, after rearrangement, only one product from the methyl)



S_N1 product (a. add from top and b. add from bottom), (after rearrangement)



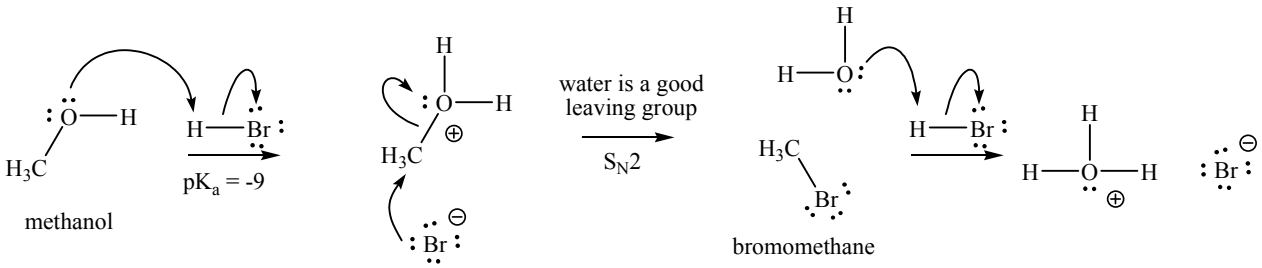
Alcohols in strong acid = Protonated Alcohols - Water as a Good Leaving Group

We can make the hydroxyl group of an alcohol, OH, into a good leaving group in strong acid conditions (HCl, HBr, HI and H_2SO_4). Strong protic acids are used to extensively protonate the alcohol OH. When the alcohol OH is protonated, the leaving group is water, not hydroxide. Water's conjugate acid is H_3O^+, ($pK_a = -2$), while hydroxide's conjugate acid is H_2O, ($pK_a = 16$). If substitution is the desired goal, then the strong halide acids are normally used, HCl, HBr or HI. If elimination is the desired goal, then concentrated sulfuric acid (H_2SO_4) is used at an elevated temperature (Δ).

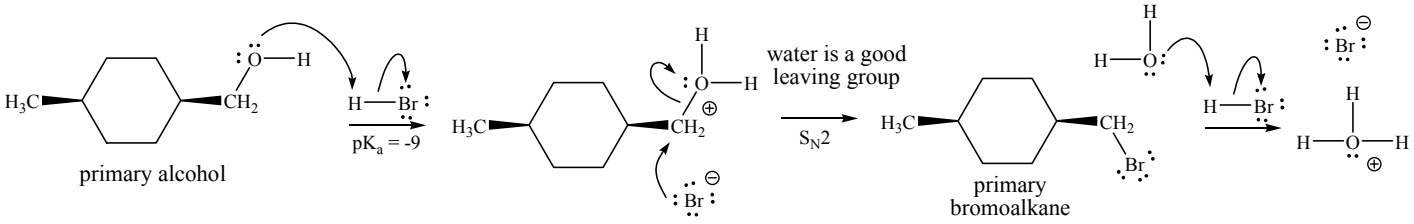
Using the hydrohalic acids (HCl, HBr or HI), very polar, strongly acidic conditions encourage S_N1 reactions, and these are assumed to be operating at all tertiary and secondary alcohol (ROH) centers. Rearrangements are frequently observed under these conditions. The large energy expense of a methyl or primary carbocation prevents the escape of water on its own. The H_2O at methyl and primary ROH_2^+ is assumed to be pushed off by the halide (S_N2) of the strong acid to form a methyl or primary haloalkane without rearrangement.

a. 1°, 2° and 3° ROH reacted with HX acids (HCl, HBr, HI) - usually S_N chemistry

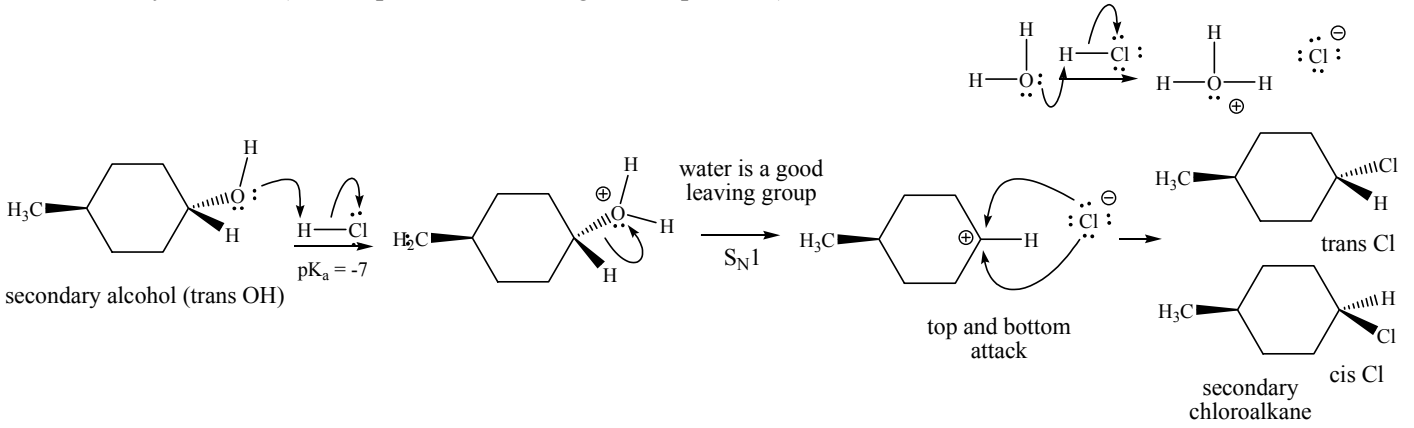
i. methyl alcohols (S_N2 emphasized, no rearrangement)



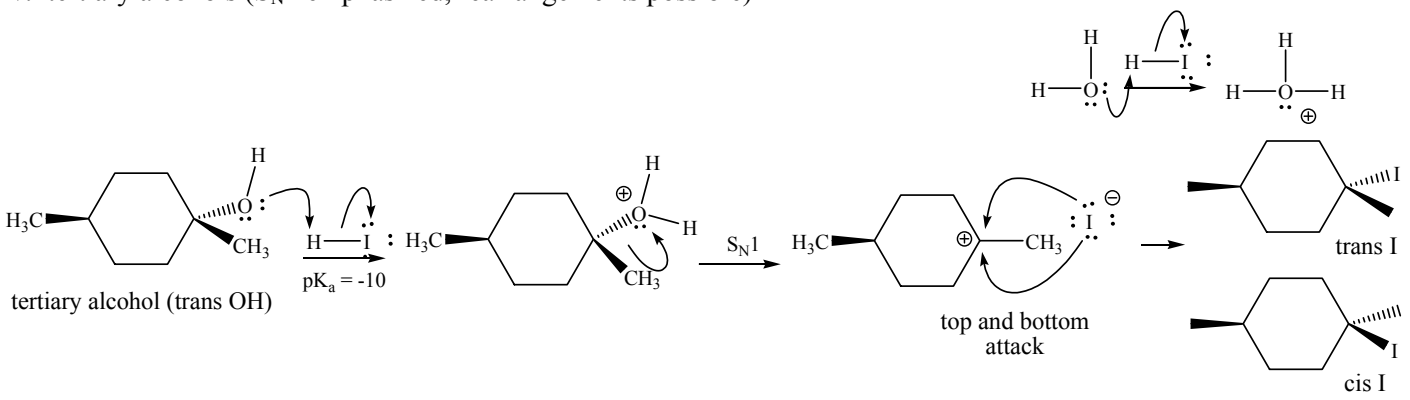
ii. primary alcohols (S_N2 emphasized, no rearrangement)



iii. secondary alcohols (S_N1 emphasized, rearrangements possible)



iv. tertiary alcohols (S_N1 emphasized, rearrangements possible)

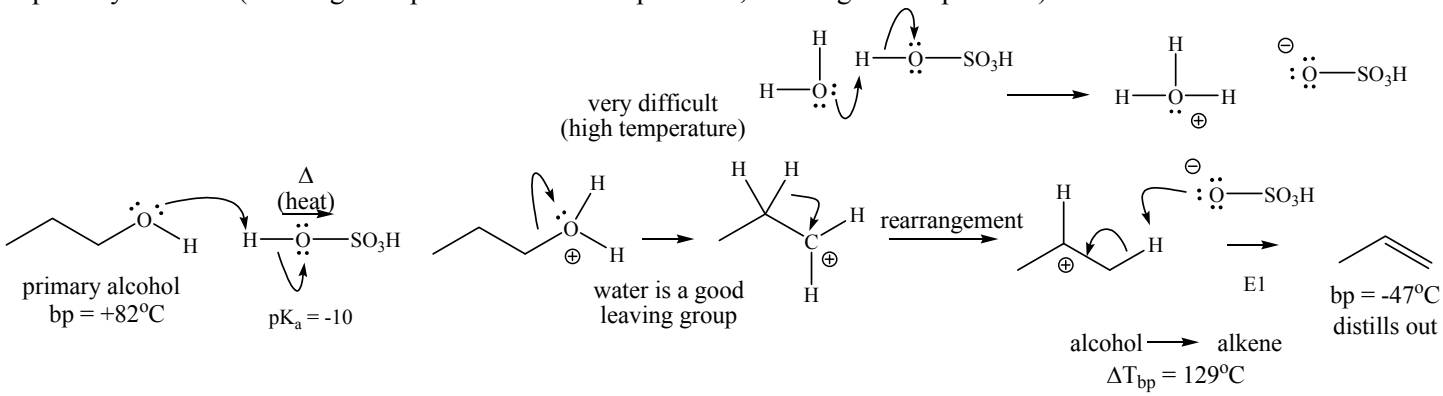


Problem 29 - Propose a synthesis of monodeuterated cyclohexane from cyclohexanol.

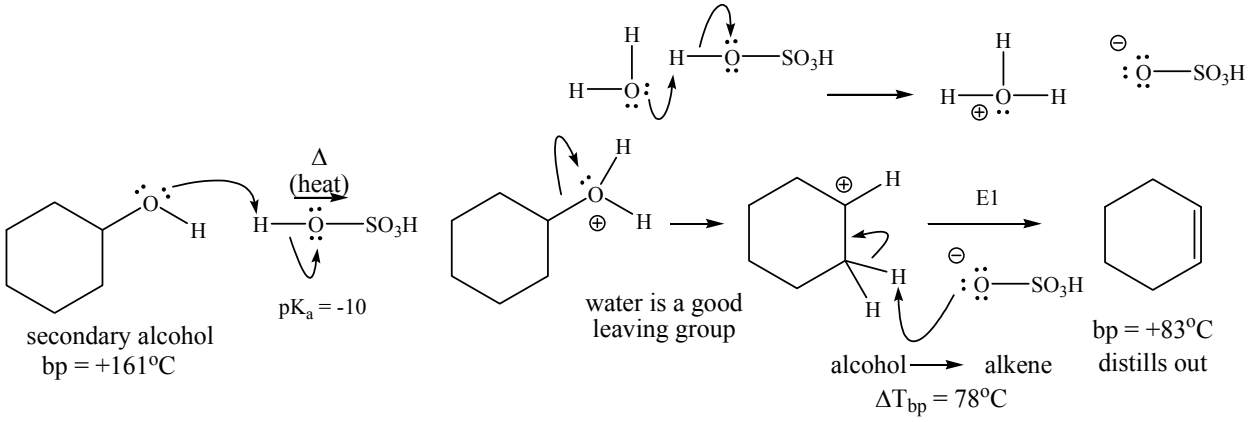
b. 1°, 2° and 3° ROH reacted with H_2SO_4 and high temperature = E1 chemistry

Using strongly acidic sulfuric acid, H_2SO_4, at elevated temperatures favors E1 reactions because lower boiling alkenes distill out and continually shift the equilibrium to make more alkene, which continues to distill out, until there is no more alcohol left in the reaction pot. We will assume that an E1 mechanism is operating in all of the reactions below (even the primary alcohol, an exception to our rule about no primary carbocations – the conditions are very harsh). Rearrangements are possible and observed.

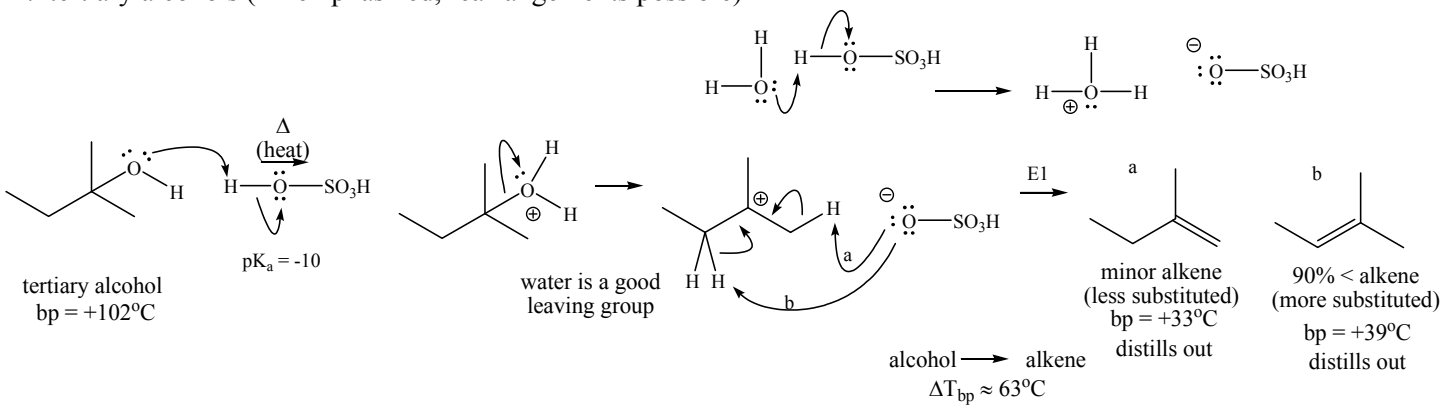
i. primary alcohols (with high temperature E1-? - emphasized, rearrangements possible)



ii. secondary alcohols (E1 emphasized, rearrangements possible)

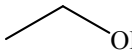
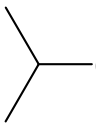
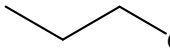
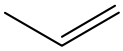
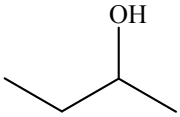
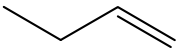
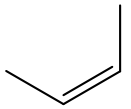
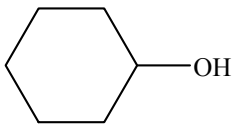
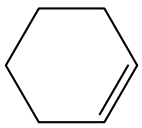


iii. tertiary alcohols (E1 emphasized, rearrangements possible)



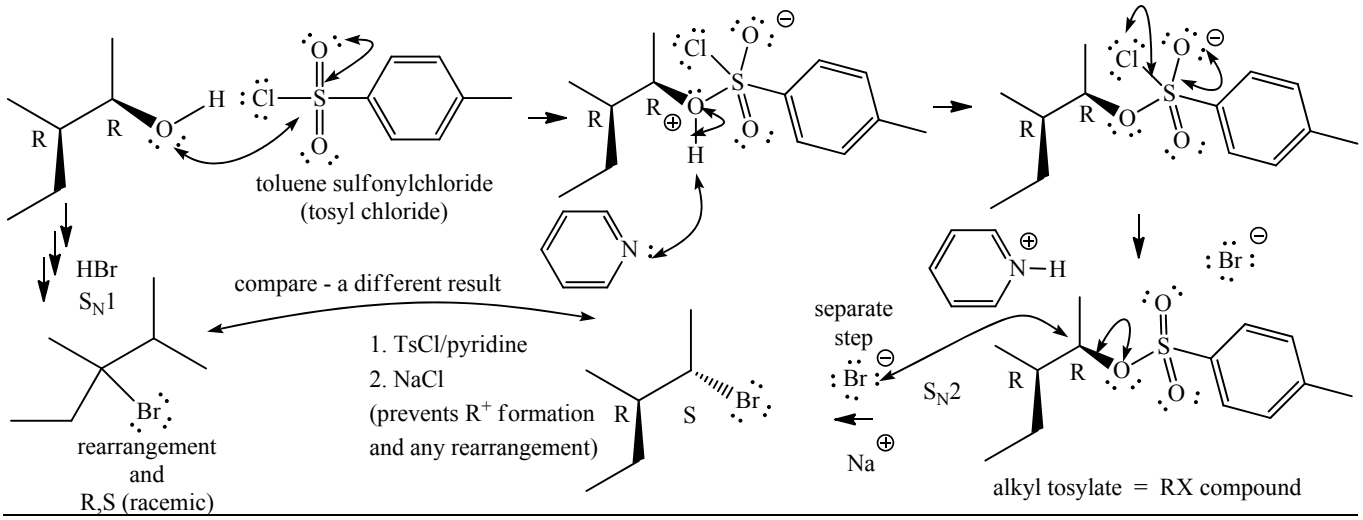
We have some, limited control to direct the alcohol functionality toward S_N or E choices. The conditions to effect these different pathways are important, so you must be aware of the details mentioned above (halide acids = S_N reactions and H_2SO_4/Δ = E1 reactions). Heat is a crucial aspect of the E1 reaction, since it allows the lower boiling alkene to escape from the reaction mixture by distillation, while the higher boiling alcohol or inorganic esters remains, in the reaction pot to reestablish equilibrium by forming more alkene, which distills.....etc. The alkene boils much lower than the alcohol it comes from because it does not have an "OH" to form hydrogen bonds.

Examples of Boiling Point Differences Between Alcohols and Possible Alkene Products

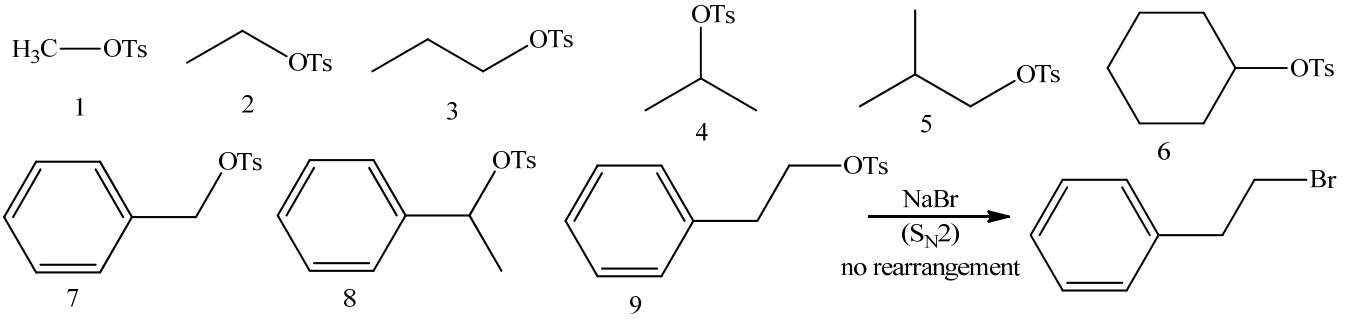
boiling points of alcohols (°C)		boiling point of alkenes (°C)		DT_{bp}
	(79 °C)	$H_2C{=}CH_2$	(-104 °C)	(183 °C)
	(82 °C)		(-47 °C)	(129 °C)
	(97 °C)		(-47 °C)	(144 °C)
	(100 °C)		(-6 °C)	(106 °C)
			(1 °C)	(99 °C)
			(4 °C)	(96 °C)
	(161 °C)		(83 °C)	(78 °C)

There are important other ways to change 'OH' into 'Br'. The OH group can be an alcohol or a carboxylic acid. Some possibilities are shown below.

1. Formation of tosylates from ROH + TsCl (toluenesulfonyl chloride = tosyl chloride), S_N/E chemistry is possible without rearrangements.

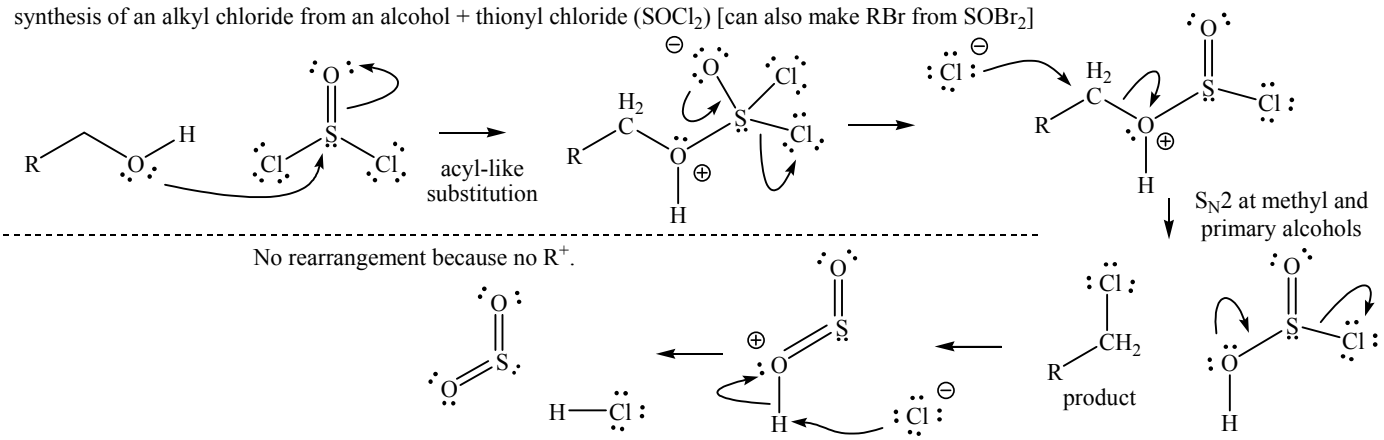


Problem 30 – We can now make the following molecules. Propose a synthesis for each. (Tosylates formed from alcohols and tosyl chloride/pyridine via acyl substitution reaction, convert "OH" from poor leaving group into a very good leaving group, similar to iodide)



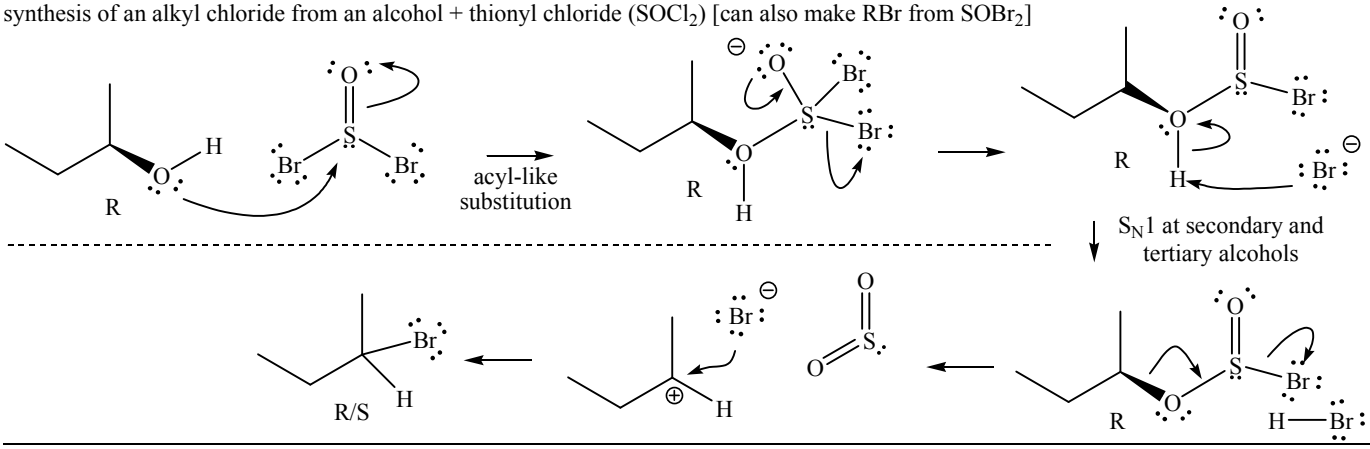
2. Other acyl-like transformations include thionyl chloride ($SOCl_2$) or thionyl bromide ($SOBr_2$) with alcohols (makes R-Cl and R-Br) or carboxylic acids (makes acid chlorides, RCOCl). Acid chlorides formed can make esters, amides and anhydrides.

Thionyl chloride with methyl, 1° ROH = acyl-like substitution at $SOCl_2$, then S_N2 at methyl and primary RX.

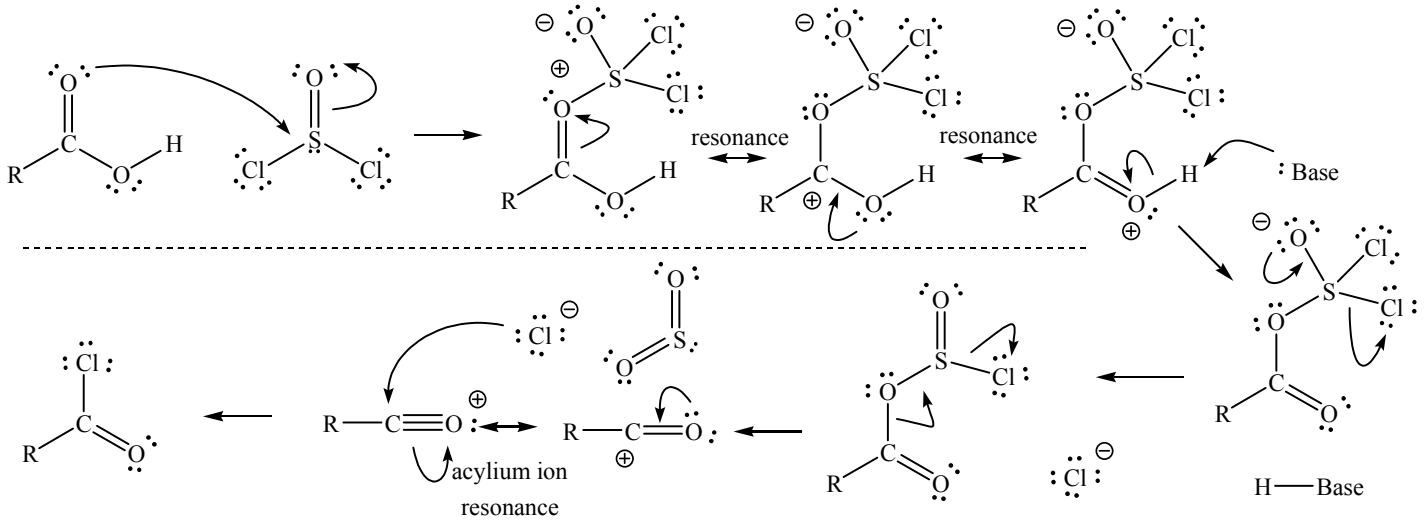


Thionyl chloride with 2° and 3° ROH = acyl substitution, then S_N1 (there are various ways you can write this mechanism)

synthesis of an alkyl chloride from an alcohol + thionyl chloride ($SOCl_2$) [can also make RBr from $SOBr_2$]

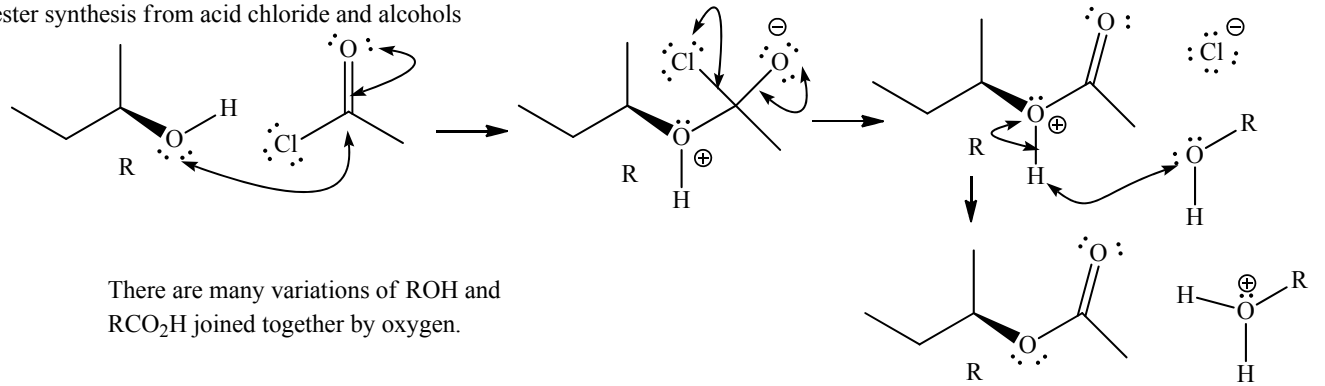


Synthesis of acid chlorides from acids + thionyl chloride ($SOCl_2$), use the carbonyl oxygen instead of the OH.



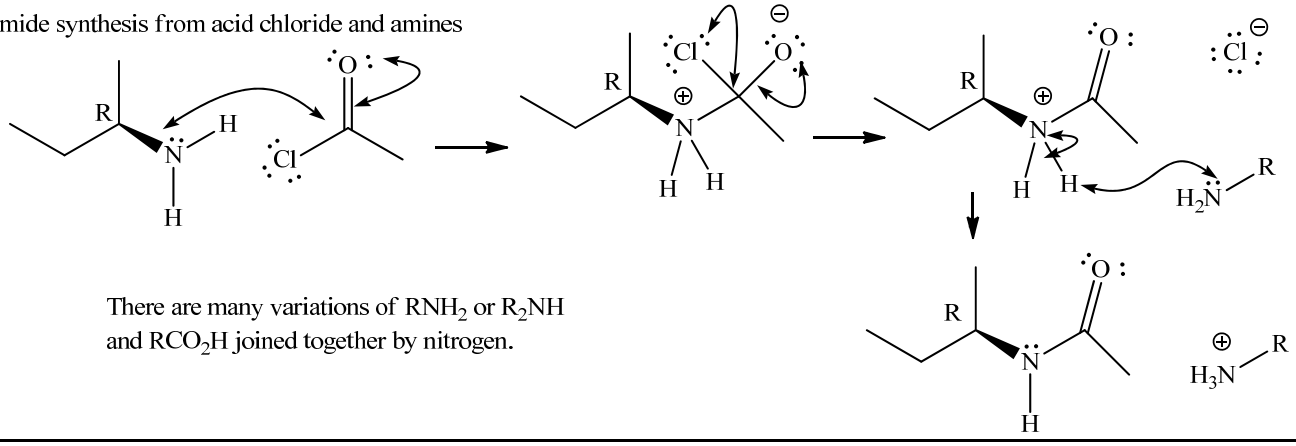
Formation of esters from ROH + acid chlorides, amides from RNH_2 or R_2NH + acid chlorides and anhydrides from RCO_2H + acid chlorides

ester synthesis from acid chloride and alcohols



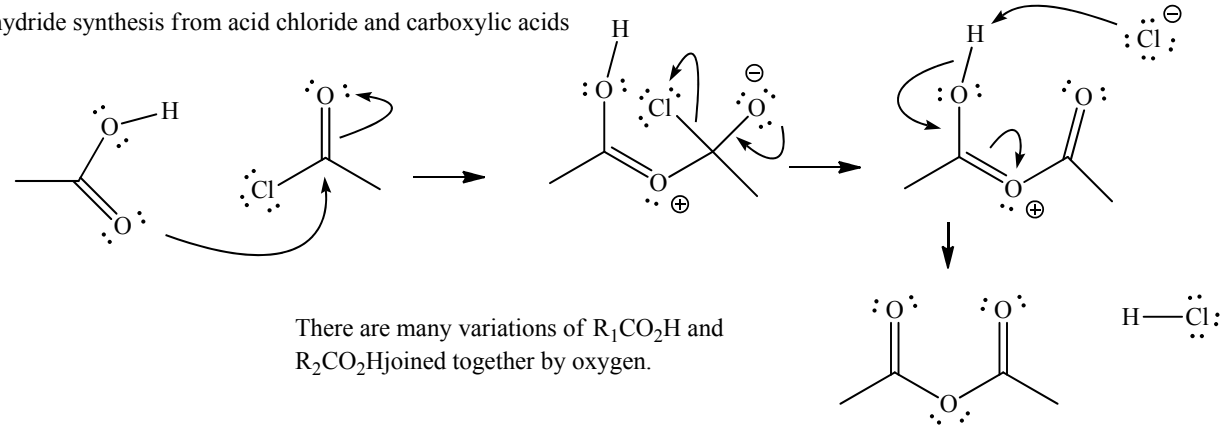
There are many variations of ROH and RCO_2H joined together by oxygen.

amide synthesis from acid chloride and amines



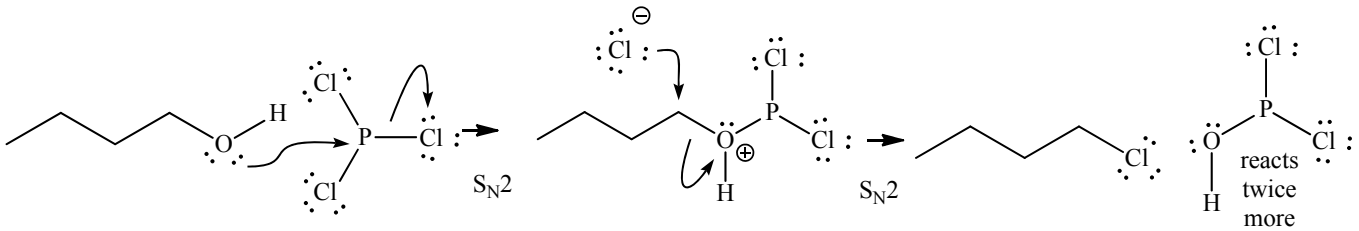
There are many variations of RNH_2 or R_2NH and RCO_2H joined together by nitrogen.

anhydride synthesis from acid chloride and carboxylic acids



There are many variations of R_1CO_2H and R_2CO_2Hjoined together by oxygen.

Phosphorous trichloride (PCl_3) = S_N2 of alcohol at phosphorous, then S_N2 (at methyl and primary $R(OH)PCl_2$)



Phosphorous tribromide (PBr_3) = S_N2 of ROH at phosphorous, then S_N1 (at secondary, tertiary, allylic and benzylic $R(OH)PBr_2$)

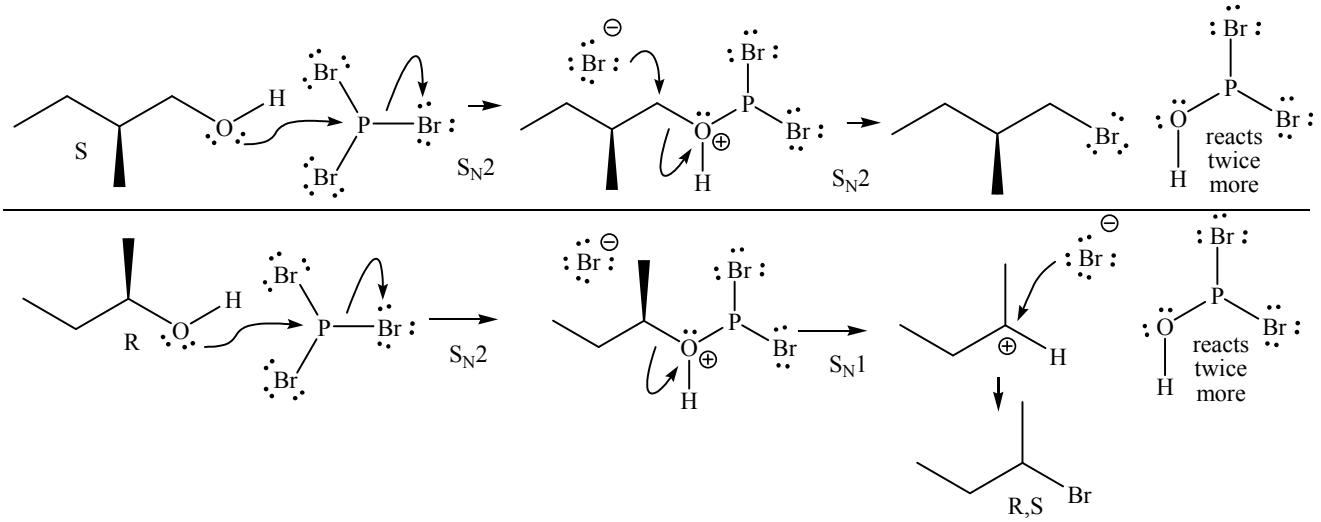
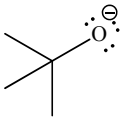
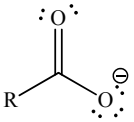
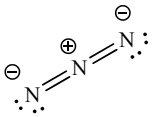
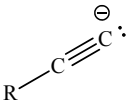
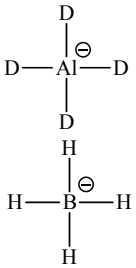
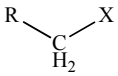
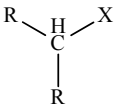
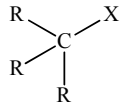
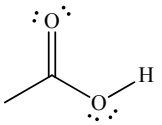
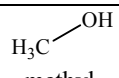
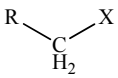
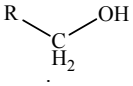
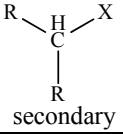
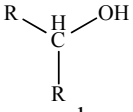
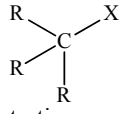
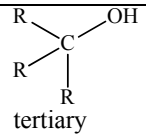


Chart of S_N and E Chemistry (note exceptions)

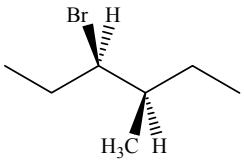
typical strong base nucleophiles are: (for our course)			 t-butoxide							
 methyl	only S_N2	only S_N2	only S_N2	only S_N2	only S_N2	only S_N2	only S_N2	only S_N2	only S_N2	only S_N2
 primary	$S_N2 > E2$	$S_N2 > E2$	$E2 > S_N2$ **exception (bulky & basic)**	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$
 secondary	$E2 > S_N2$ **exception (too basic)**	$E2 > S_N2$ **exception (too basic)**	$E2 >> S_N2$ **exception (bulky & basic)**	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$	$S_N2 > E2$	$E2 > S_N2$ **exception (too basic)**	$S_N2 > E2$
 tertiary	only E2	only E2	only E2	only E2	only E2	only E2	only E2	only E2	only E2	NA

typical weak base nucleophiles are: (for our course)				alcohol reactions in strong acid: (for our course)	 (X = Cl, Br or I)	$SOCl_2$ PCl_3 $SOBr_2$ PBr_3	1. TsCl/py 2. NaBr	H_2SO_4 Δ
 methyl	no reaction	no reaction	no reaction	 methyl	S_N2	S_N2	S_N2	not discussed
 primary	no reaction	no reaction	no reaction	 primary	S_N2	S_N2	S_N2	E1
 secondary	$S_N1 > E1$	$S_N1 > E1$	$S_N1 > E1$	 secondary	S_N1	S_N1	S_N2	E1
 tertiary	$S_N1 > E1$	$S_N1 > E1$	$S_N1 > E1$	 tertiary	S_N1	S_N1	NA	E1

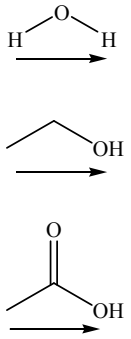
Problem 31– Look back at the table of R-Br structures on page 2. Include stereoisomers together. Be able to list any relevant structures under each criteria below.

1. Isomers that can react fastest in S_N2 reactions
2. Isomers that give E2 reaction but not S_N2 with sodium methoxide
3. Isomers that react fastest in S_N1 reactions
4. Isomers that can react by all four mechanisms, S_N2, E2, S_N1 and E1 (What are the necessary conditions?)
5. Isomers that might rearrange to more stable carbocation in reactions with methanol.
6. Isomers that are completely unreactive with methoxide/methanol
7. Isomers that are completely unreactive with methanol, alone.

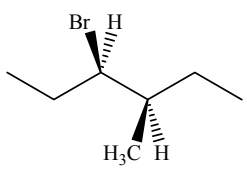
The number of each type of product (S_N1, E1, S_N2, E2) is listed after a reaction arrow for each starting structure (assuming I analyzed the possibilities accurately in my head, while sitting at the computer). Do you agree with these numbers? Can you draw a valid mechanism for each one?

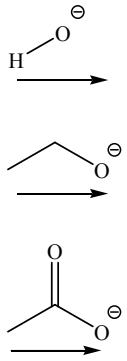


a. initial carbocation
b. after rearrangement

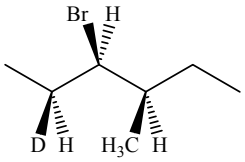


	S_N1	E1
a.	2	4
b.	2	5
a.	2	4
b.	2	5
a.	2	4
b.	2	5

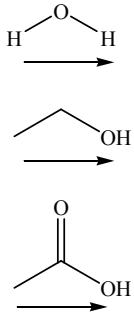




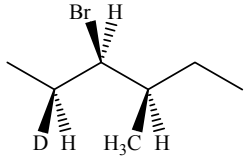
S_N2	E2
1	3
1	3
1	3

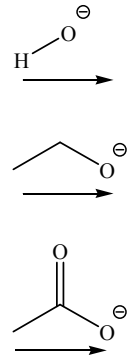


a. initial carbocation
b. after rearrangement



	S_N1	E1
a.	2	6
b.	2	5
a.	2	6
b.	2	5
a.	2	6
b.	2	5



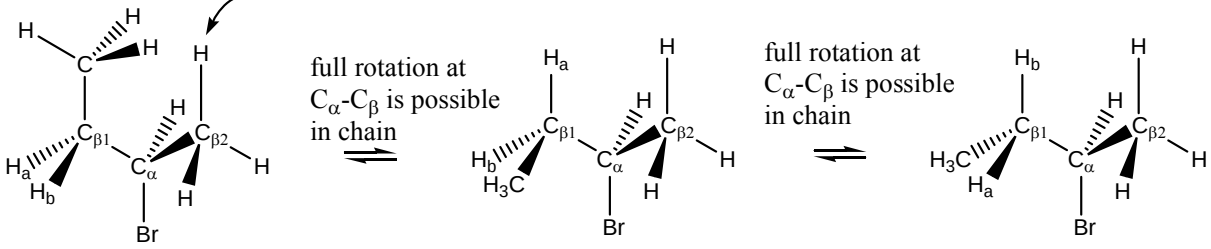


S_N2	E2
1	3
1	3
1	3

Similar patterns in cyclohexane RX structures. The leaving group has to be axial in S_N2 and E2 reactions.

When methyl on $C_\beta1$ is anti to C-Br, no S_N2 is possible and no E2 is possible from $C_\beta1$.

Rotation of C_α-$C_{\beta1}$ brings H_a or H_b anti to C-Br, which allows S_N2 and two different E2 possibilities: H_a (Z) and H_b (E). Since $C_{\beta2}$ is a simple methyl, there is no $C_{\beta2}$ substituent to inhibit either of these reactions.



No S_N2 possible and no E2 from $C_{\beta1}$, but E2 from $C_{\beta2}$ (1-butene) is possible.

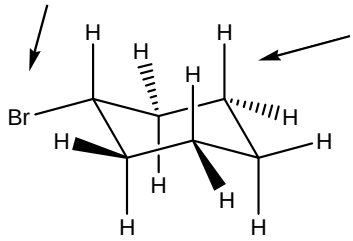
S_N2 possible
E2 from $C_{\beta1}$ (2Z- butene)
E2 from $C_{\beta2}$ (1-butene)

S_N2 possible
E2 from $C_{\beta1}$ (2E- butene)
E2 from $C_{\beta2}$ (1-butene)

alkene stabilities ⇒ tetrasubstituted > trisubstituted > trans-disubstituted > gem-disubstituted ≈ cis-disubstituted > monosubstituted

Use these ideas to understand cyclohexane reactivity.

equatorial leaving group



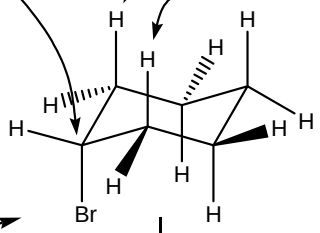
No S_N2 is possible (1,3 diaxial positions block approach of nucleophile), and no E2 is possible because ring carbons are anti.

only partial rotation is possible in ring

No S_N2 or E2 when "X" is in equatorial position.

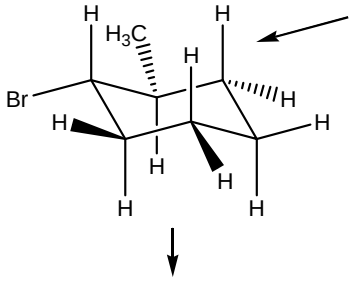
S_N2 possible if C_α is not tertiary and there is no anti C_β "R" group.

E2 possible with anti C_β-H.



axial leaving group

Both S_N2 and E2 are possible in this conformation with leaving group in axial position.



No S_N2 is possible (1,3 diaxial positions block approach of nucleophile), and no E2 is possible because ring carbons are anti.

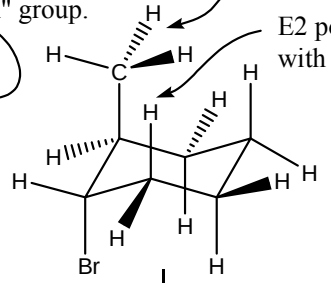
only partial rotation is possible in ring

No S_N2 or E2 when "X" is in equatorial position.

No S_N2 possible if there is an anti C_β "R" group.

No E2 possible, no anti C_β-H.

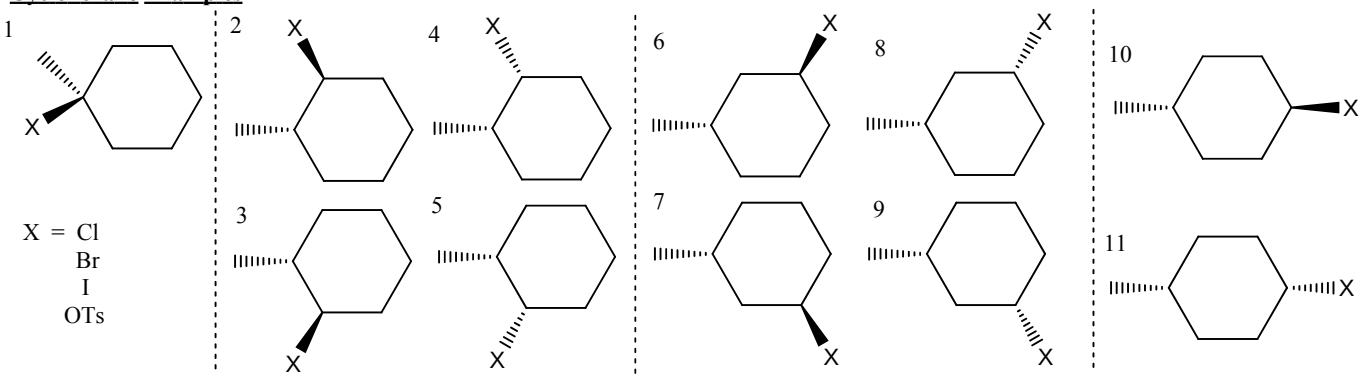
E2 possible with anti C_β-H.



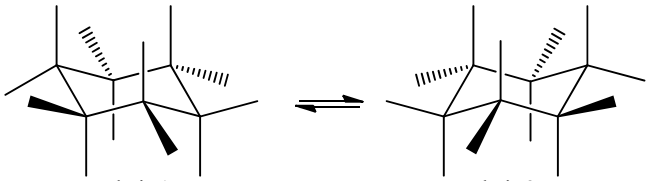
Only E2 is possible in this conformation. Leaving group is in axial position.

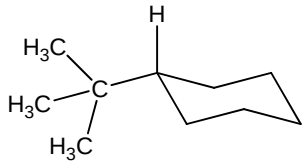
Problem 32 – Predict possible products of a. water and b. ethanoate (acetate) with structures 2, 10 and 13. Only consider rearrangements to more stable carbocations where appropriate.

Cyclohexane Examples



1. Which conformation is reactive?
2. Is S_N2 possible? Requires an open approach at C_α and C_β.
3. Is E2 possible? Requires anti C_β-H.
4. How many possible products are there?
5. What is the relationship among the starting structures?
6. What is the relationship among the products?
7. Are any of the starting structures chiral?
8. Are any of the product structures chiral?

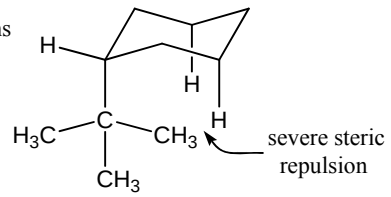


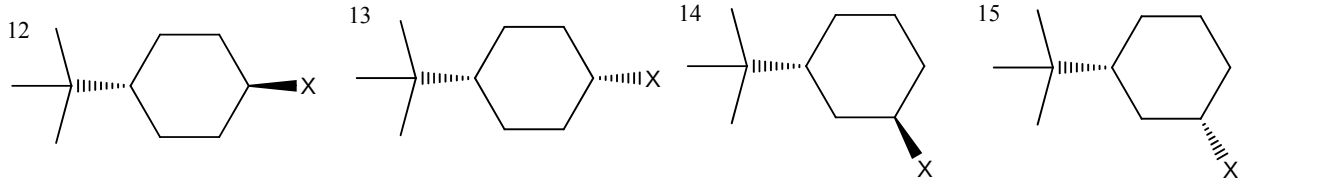


t-butyl substituent locks in chair conformation with equatorial t-butyl

Cyclohexane structures have two chair conformations possible.

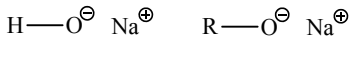
$K_{eq} \approx \frac{1}{9{,}999}$

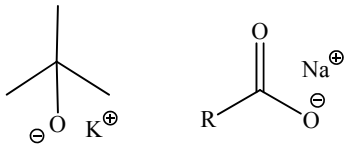




Mechanism predictions with:

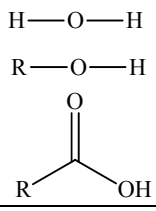
Some examples



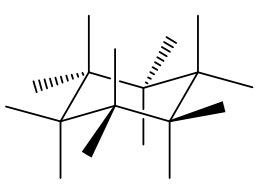


strong nucleophile/bases + other anions shown above

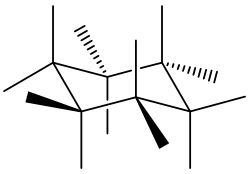
weak nucleophiles



The number of each type of product (S_N1, E1, S_N2, E2) is listed after a reaction arrow for each starting structure (assuming I analyzed the possibilities accurately in my head, while sitting at the computer). Only consider rearrangements in part 9. Do you agree with these numbers? Can you draw a valid mechanism for each one?



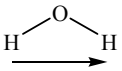
chair 1



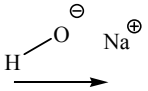
chair 2

Only consider carbocation rearrangements that immediately go to a more stable carbocation (not equally stable carbocations = too many possibilities)

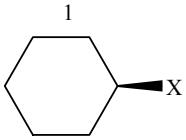
condition 1



condition 2

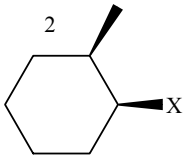


1



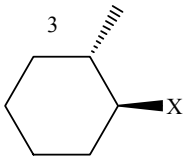
S_N1	E1	S_N2	E2
1	1	1	1

2



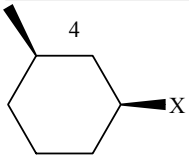
	S_N1	E1	S_N2	E2
a.	2	2	1	2
b.	1	2		

3



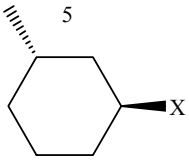
	S_N1	E1	S_N2	E2
a.	2	2	0	1
b.	1	2		

4



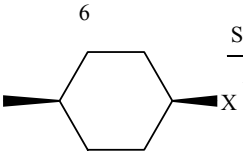
S_N1	E1	S_N2	E2
2	2	1	2

5



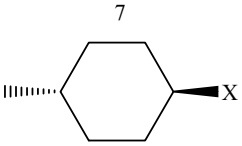
S_N1	E1	S_N2	E2
2	2	1	2

6



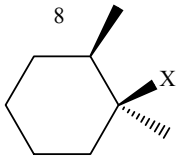
S_N1	E1	S_N2	E2
2	2	1	2

7



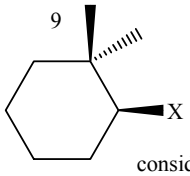
S_N1	E1	S_N2	E2
2	2	1	2

8



S_N1	E1	S_N2	E2
2	3	0	3

9

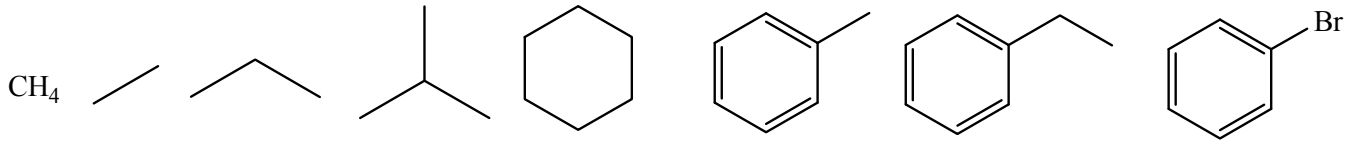


	S_N1	E1	S_N2	E2
a.	2	1	0	1
b.	4	5		
c.	1	2		
d.	1	2		

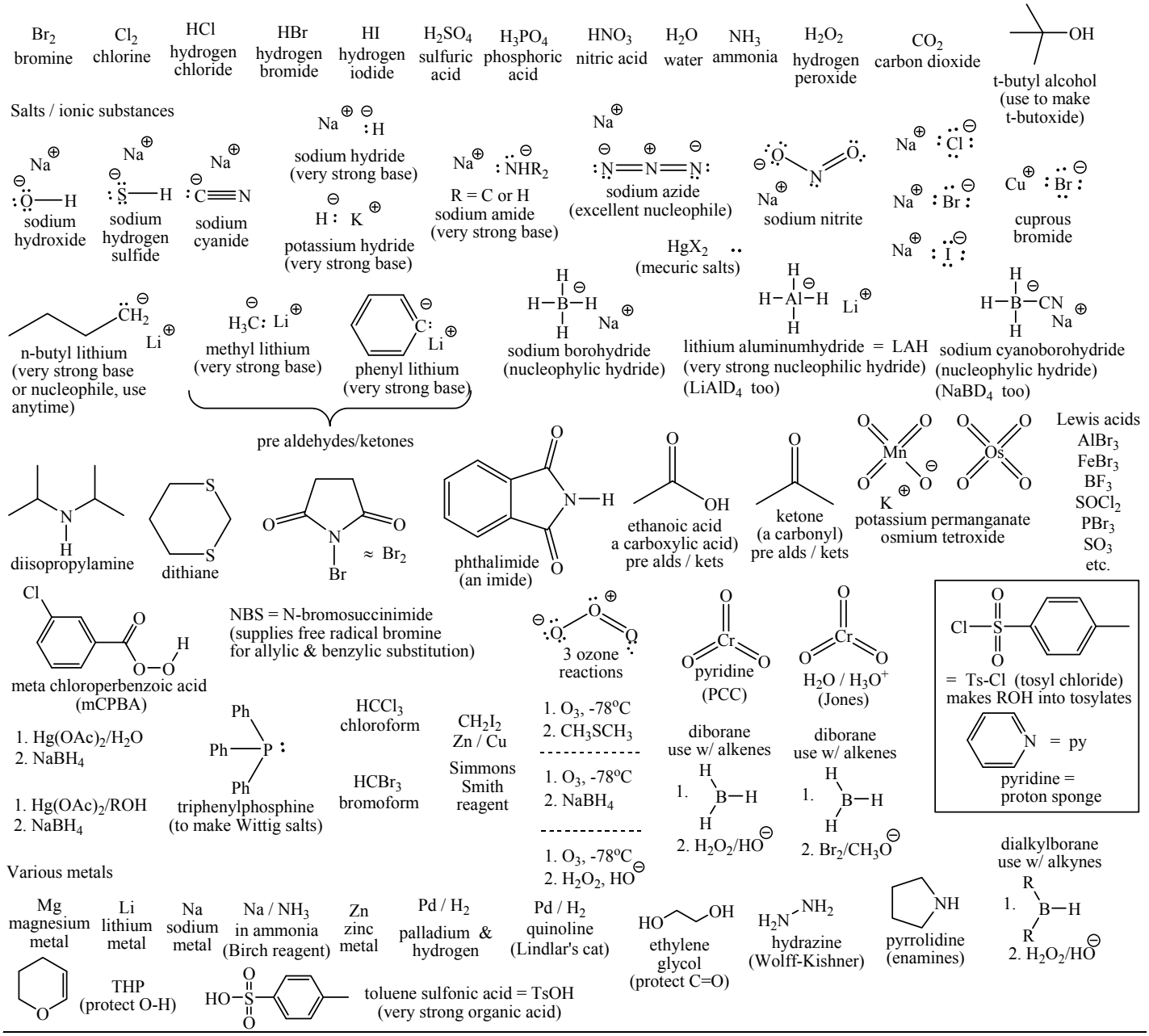
consider any 3° R^+ possibility and consider stereoisomers

Available chemicals from the catalog

Sources of carbon - you can invoke these whenever needed:

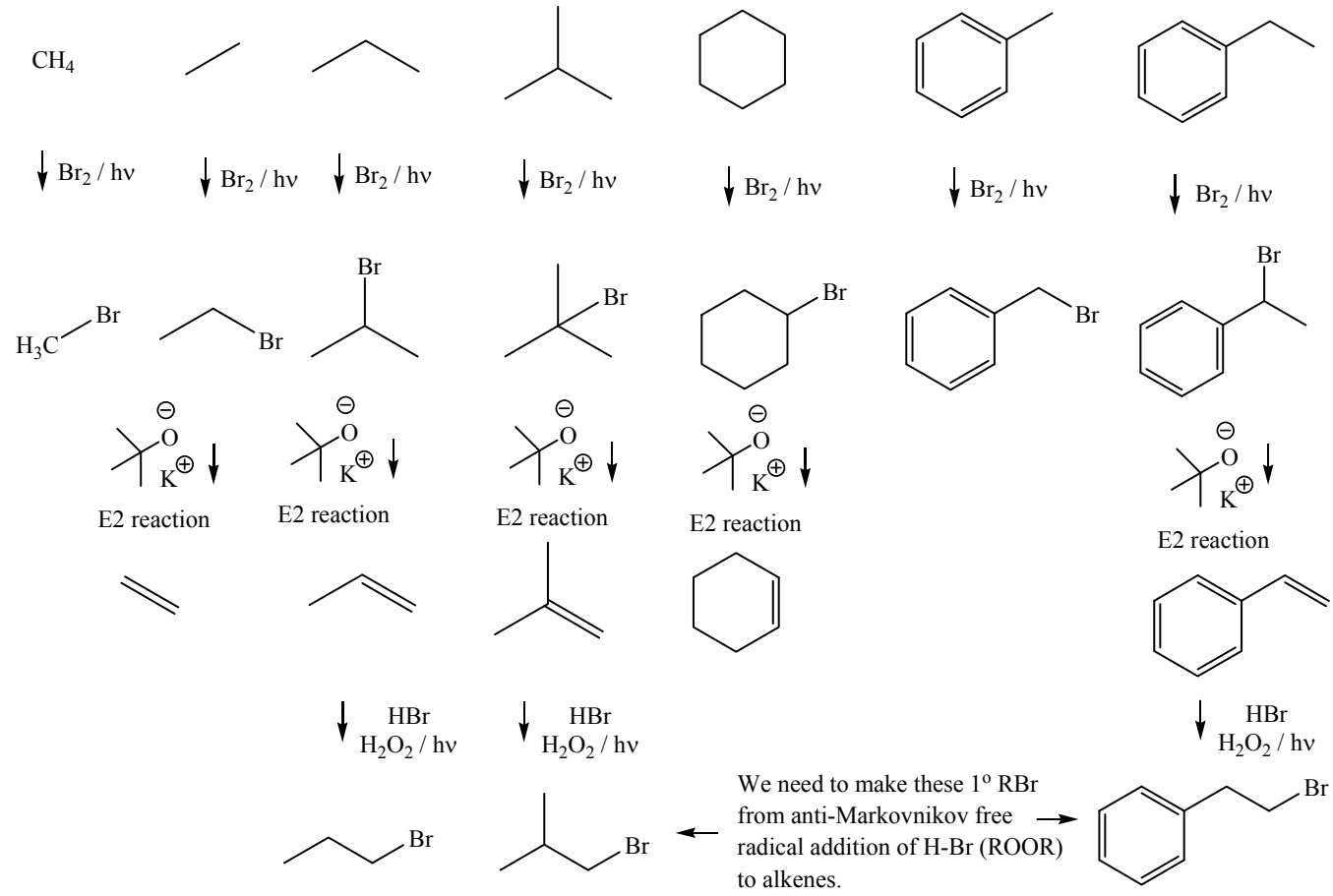


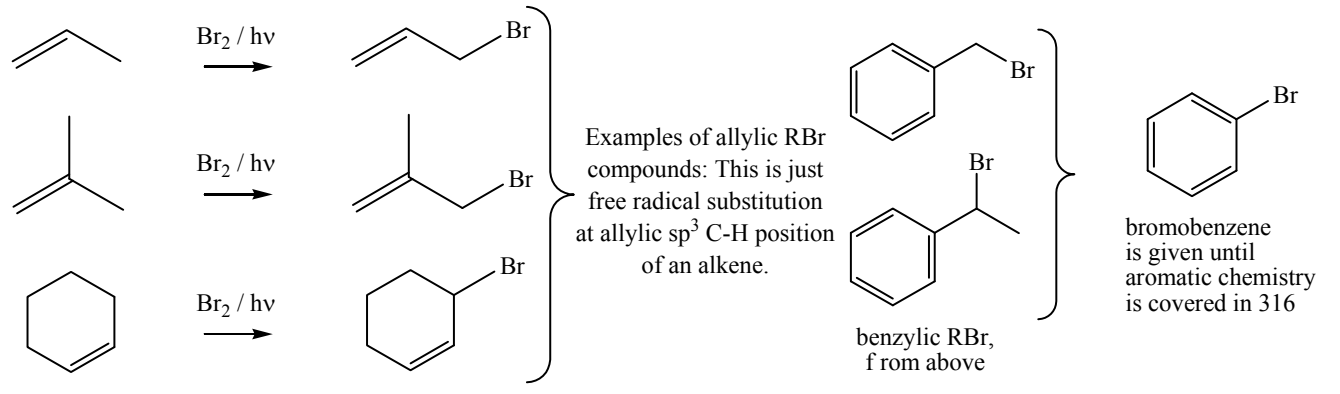
Commercially available chemicals and reagents - you can invoke these whenever you need them.

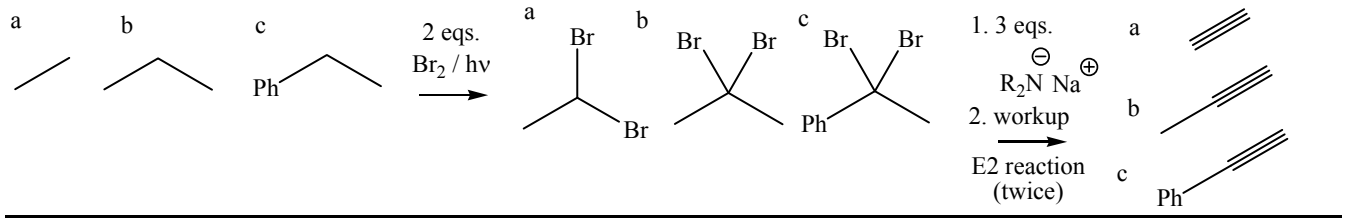


For now, the structures below represent your hydrocarbon starting points to synthesize target molecules (TM) that are specified. We will only study two free radical reactions in our course, but they are very important reactions because they make versatile functionalized starting molecules for synthesis of all the other functional groups studied in this course.

Allowed starting structures – our main sources of carbon – 1. Free radical substitution of sp^3 C-H bonds to form sp^3 C-Br bonds at the weakest C-H position and 2. Anti-Markovnikov addition to alkenes makes 1° R-Br. From these two reactions we can make 13 R-Br molecules below.



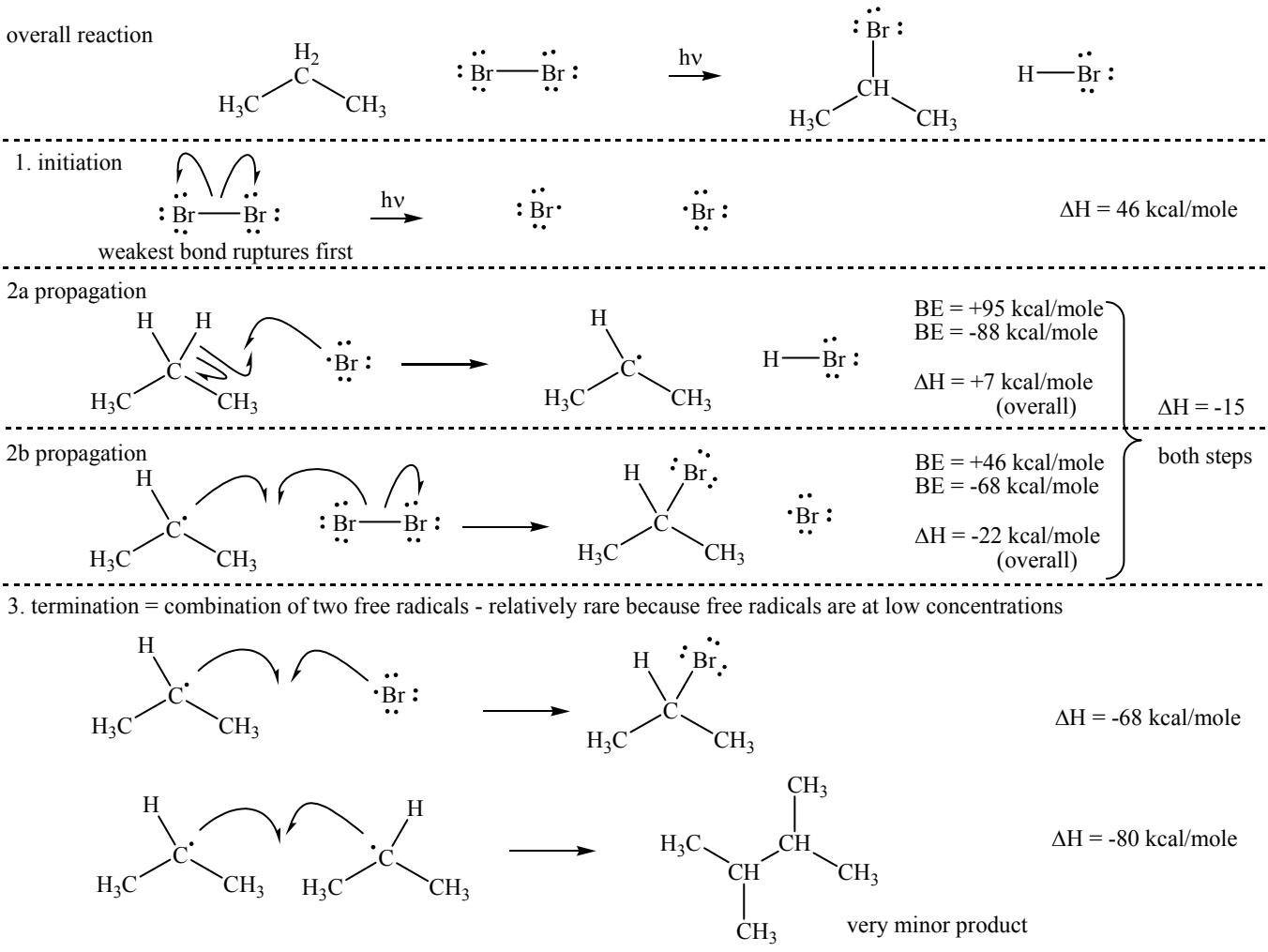




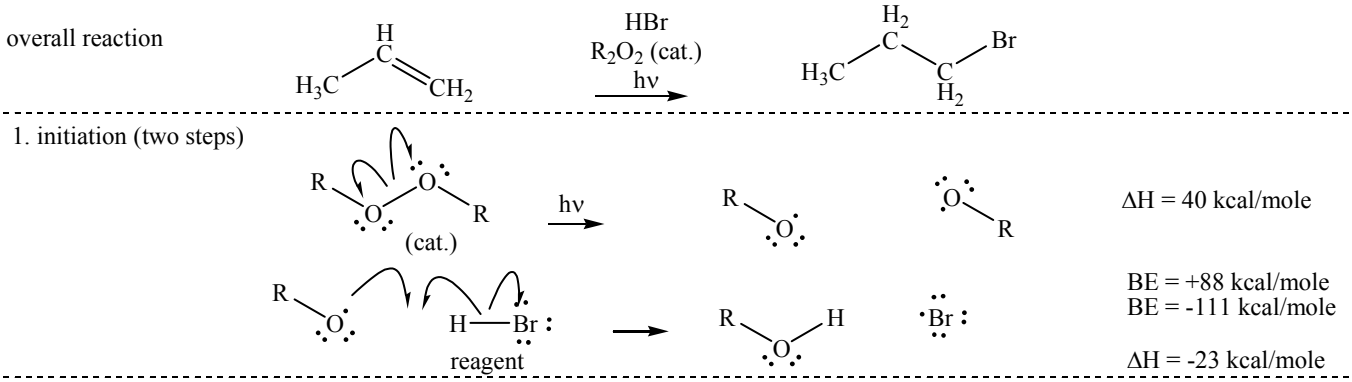
You will need to propose a step-by-step synthesis for each target molecule from these given structures. Every step needs to show a reaction arrow with the appropriate reagent(s) above each arrow and the major product of each step. This is often accomplished by using retrosynthetic thinking. You start at the target molecule (the end) and work your

way backwards (towards the beginning), one step at a time until you reach an allowed starting material. The starting material of each step becomes the target molecule for the next step until you reach the beginning.

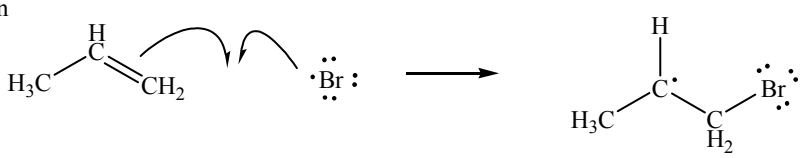
1. **Mechanism for free radical substitution of alkane sp^3 C-H bonds to form sp^3 C-Br bonds at weakest C-H position**



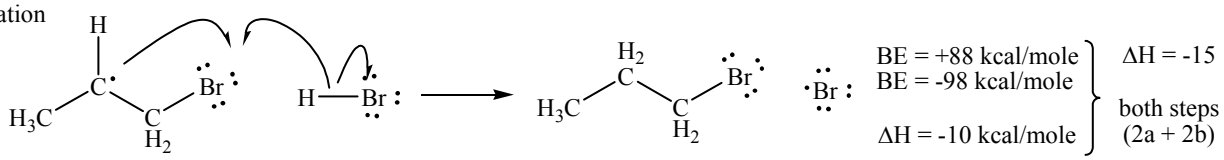
2. **Free radical addition mechanism of H-Br alkene pi bonds** (alkenes can be made from E2 or E1 reactions at this point in course) (anti-Markovnikov addition to alkenes)



2a propagation

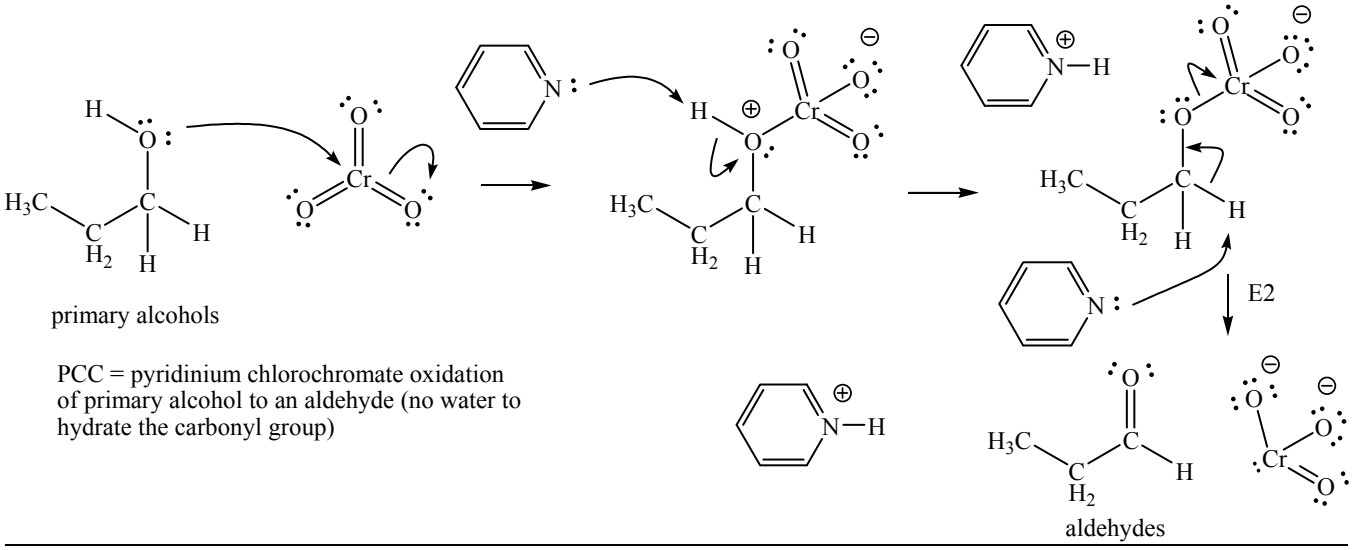


2b propagation

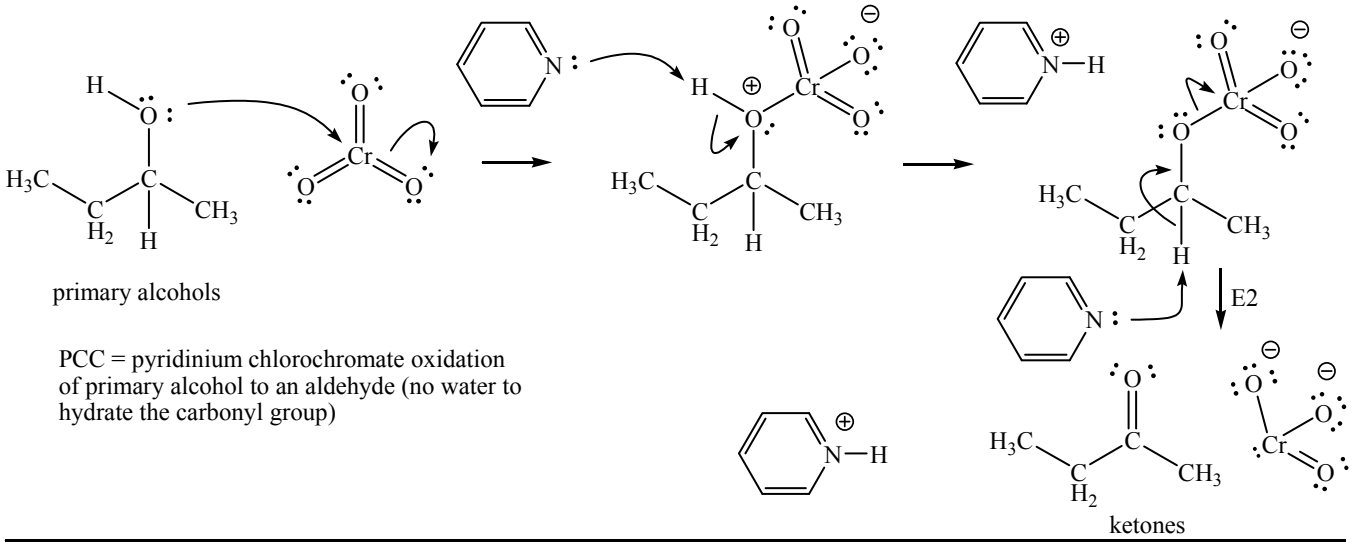


Miscellaneous E2 mechanism not included above; An E2 reaction that makes carbonyl compounds (C=O)

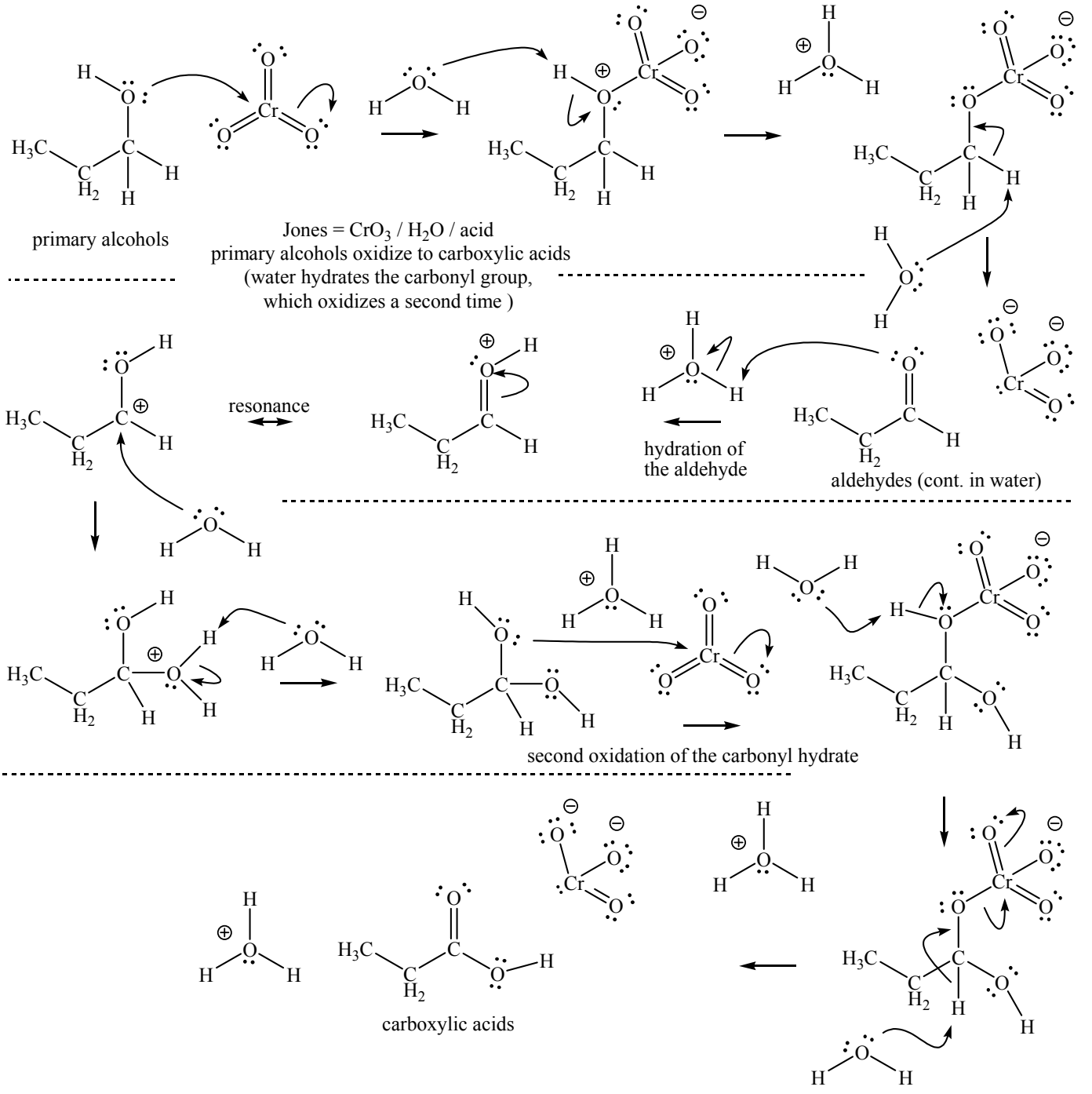
1. PCC = pyridinium chlorochromate, (CrO_3/pyridine), CrO_3 oxidations of alcohols (methyl, 1° and 2° ROH) without water. Steps are: 1. Cr=O addition, 2. acid/base and 3. E2 to form C=O (aldehydes and ketones).



CrO_3 oxidations of alcohols (methyl, 1° and 2° ROH) without water = PCC, Cr=O addition, acid/base and E2 to form C=O (aldehydes and ketones)

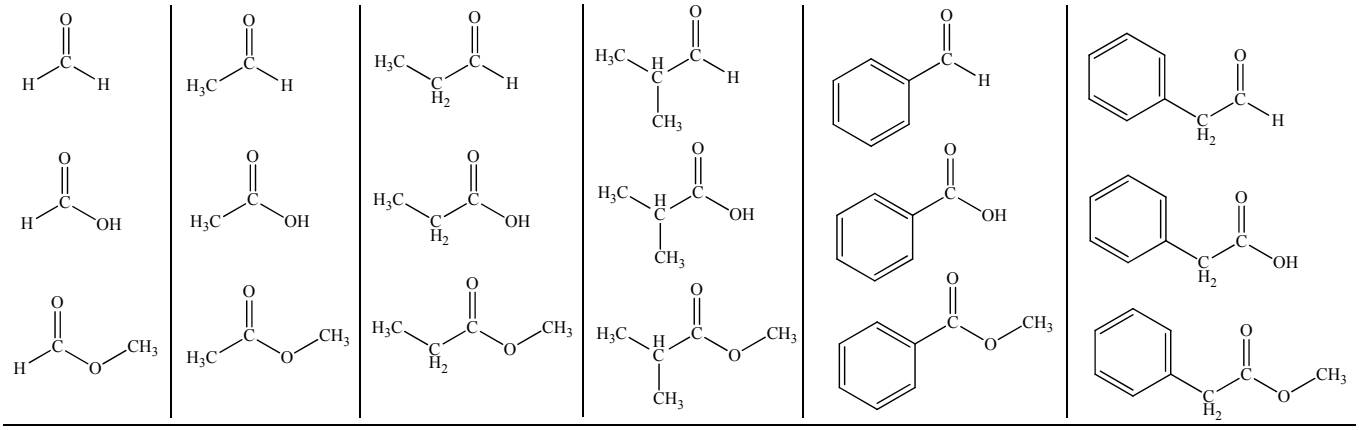


2. Jones reagent = CrO_3/water/acid, CrO_3 oxidations of alcohols (methyl, 1° and 2° ROH) with water. Steps are: 1. Cr=O addition, 2. acid/base and 3. E2 to form C=O (aldehydes and ketones) 4. hydration of C=O and repeat reactions when the starting alcohol is a 1° alcohol (forms carboxylic acids from primary alcohols and ketones from secondary alcohols).

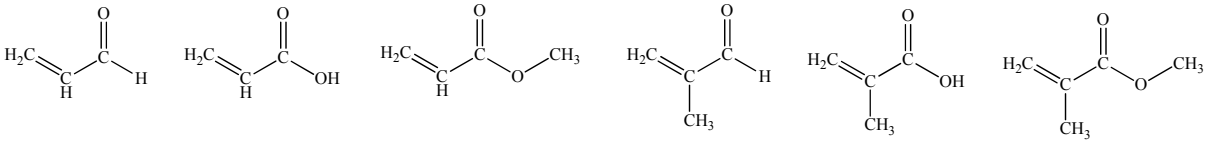


Problem 33 – We can now make the following molecules. Propose a synthesis for each from our starting materials.

aldehydes, carboxylic acids and esters



conjugated aldehydes, carboxylic acids and esters



ketones